FEBRUARY 1950

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Original Articles

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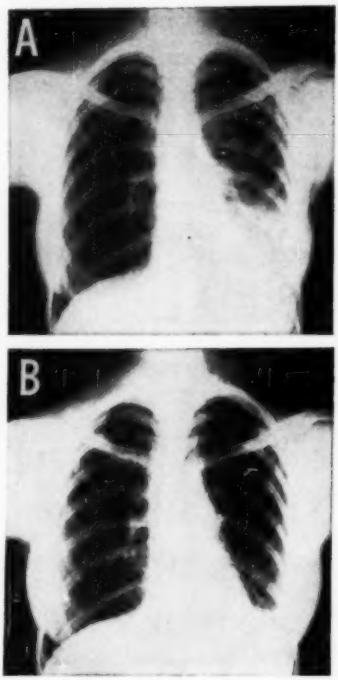

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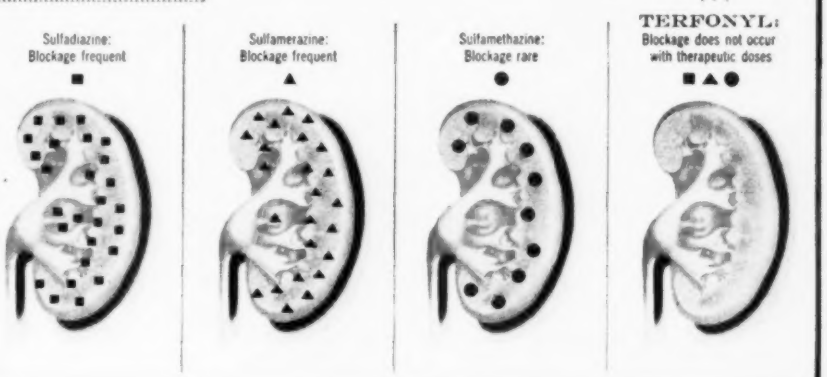

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

FEBRUARY 1950

THE ADRENAL CORTEX AND HYPERTENSION*

GEORGE A. PERERA

Associate Professor of Medicine, Columbia University, College of Physicians and Surgeons

THE rôle of the adrenal cortex, in the last few years, has been assuming tremendous proportions. Abnormal responses to stress, emotional disturbances, cancer, congestive failure and arthritis are but a few of the disorders which possess adrenal implications as judged by a perusal of current literature.

I have been asked to review the evidence concerning a relationship of the adrenal cortex to arterial hypertension. I am most grateful for this opportunity, for it will permit me to summarize our knowledge as well as to remind you of its many gaps and inadequacies.

As is so often the case, the first hint of a possible relationship between the adrenal glands and hypertension was made many years ago, forty-seven to be exact,[1] long before its substantiation by factual data of any kind. The first description of hypertensive changes secondary to an adrenal cortical tumor had been reported even earlier (1897),[2] although

* Read January 5, 1950 at the Stated Meeting of The New York Academy of Medicine.
Investigations from this laboratory were supported (in part) by research grants from the National Heart Institute, U.S.P.H.S., the Albert and Mary Lasker Foundation and the Albert H. and Jessie D. Wiggin Foundation. Desoxycorticosterone acetate was supplied by Roche-Organon, Inc., the adrenocorticotropic hormone by the Armour Co., and cortisone by Merck & Co.

little notice was given to this association until the more extensive observations of Oppenheimer and Fishberg in 1924.[3] These authors commented upon the elevated blood pressure found in patients with such tumors and contrasted it with the reduced blood pressure of Addison's disease. Today it is common knowledge that many patients with hyperadrenocorticalism may exhibit hypertension, and that with hypoadrenalism one frequently observes hypotension, even after restoration of water and electrolyte balance by appropriate therapy.

In recent years a series of separate observations has appeared, each one relating the adrenal cortex in some fashion to the regulation of blood pressure or the hypertensive state. Let us review this material first as developed in animal experimentation, then as studied in the human.

Animal Observations

Goldblatt[4] made the initial discovery that *bilateral* (but not subtotal) *adrenalectomy interfered with the development or maintenance of experimental renal hypertension.* Comparable reports were made by Blalock and Levy,[5] Page,[6] Collins and Wood[7] and others.[8-18] Adrenalectomy, some of these workers noted, was associated with a fall in the concentration of hypertensinogen and at times a reduction in the response to renin. The administration of desoxycorticosterone restored the hypertension, and one investigator observed a similar restoration of the blood pressure on giving cortisone.[17] Adrenalectomy also modified the hypertension produced in dogs by the intracisternal injection of kaolin,[19] in rats by auditory stimulation[20] and, again in rats, by the injection of dehydroxyphenylalenine.[21]

Despite the apparent consistency of these results, Rogoff, Nixon and Stewart[22] claimed that the blood pressure remained high in three hypertensive dogs four to nine days after adrenalectomy. It is difficult to maintain the weight and sometimes the well-being of animals after adrenalectomy. Hence the possibility must be borne in mind that earlier experiments were too acute or included animals that were in poor condition. It is still conceivable that at least some forms of experimental renal hypertension can be achieved in the absence of the adrenal glands.

Even the *juxtaglomerular apparatus of the kidney* has been related to the adrenals. Goormaghtigh[23] suggested that this apparatus might secrete renin or some other vasopressor material. He also reported that the hypertension, produced by section of the depressor nerves, was asso-

ciated with thickening of the adrenal cortex together with an increased adrenal cholesterol content.[24] Dougherty[25] has remarked that large dosages of adrenocorticotropic hormone may stimulate the development of the juxtaglomerular apparatus, and stated that Rich had observed a marked increase in the production of the afibrillar cells of these structures in a patient having an adrenal cortical tumor.

The recently-described *vasotropic principles of renal and hepatic origins* give rise to yet another example of adrenal cortical relationship in experimental renal hypertension.[26] Shortly after the partial constriction of the renal artery by a Goldblatt clamp, vaso-excitor materials appear in the circulation but are subsequently counterbalanced by increasing amounts of vaso-depressor agents. A similar state of equilibrium with high titers exists in patients with essential hypertension.[27] Adrenalectomy abolishes or impairs the renal capacity to form the vaso-excitor materials under anaerobic conditions *in vitro* even in animals maintained on high salt diets, but the combination of desoxycorticosterone acetate and salt restores normal kidney behavior.[28-30]

Victor[31] produced hypertension in dogs by *unilateral ligation of the periadrenal blood vessels and tissue*. Although others have attempted to reproduce the experiment, there has been as yet only equivocal support of this interesting study.[32]

That *epinephrine injection is followed by an enhanced output of cortical hormone* has been described by Vogt.[33] This deserves mention here only because of the fact that chronic as well as paroxysmal hypertension may be evident in patients with pheochromocytomata.[34] Studies on the hemodynamic effects of epinephrine and nor-epinephrine, both of which occur in the adrenal medula, have been reported by Goldenberg *et al.*[35,36]

Next let us recall that the adrenal cortex is intimately concerned with *sodium metabolism*. Although the mechanism of the depressor action of salt restriction in hypertensive disease has not been explained, animal studies have suggested that electrolytes and water may behave differently in the presence of hypertension. For example, rats with experimental renal hypertension show significant degrees of polydipsia and polyuria[37] and tend to reduce their sodium intake when allowed freedom of choice.[38] Tissue studies in hypertensive dogs imply that muscle sodium may be elevated at the expense of intracellular potassium.[39] Furthermore, rats with an elevated blood pressure induced by renal manipulation

have an increased ratio of serum sodium to chloride.[40] Grollman and Harrison[41] found that a rice diet exerted a pronounced blood pressure-lowering effect (blocked by the addition of sodium chloride) and an extension of the percentage survival in hypertensive rats. It was even claimed that the adrenals of rats on a restricted sodium intake were smaller and different in color.[42] In contrast to these studies, the addition of salt to the diet has been accompanied, except in chickens,[43, 44] by slight or no increases in the blood pressure of normal animals.[45]

Elevation of blood pressure following the *administration of various sterols* has been reported by some workers and denied by others.[46-51] The complexities of accurate blood pressure measurement, the need for more adequate controls and problems of dosage make it difficult to evaluate some of these studies. Nevertheless, they lead us to the final chapter to date in the story of animal experimentation, which deals with the pressor properties of specific steroids of probable adrenal derivation.

Toxic effects of *desoxycorticosterone esters* in dogs were noted in 1939 by Kuhlmann, Ragan, Ferrebee, Atchley and Loeb.[52] In two animals, receiving 20 mgs. of desoxycorticosterone acetate daily for 70 days, a small rise in systolic blood pressure was recorded. Since that time many experimenters have observed a rise in arterial tension often to abnormal levels following the sustained administration of this steroid.[48, 53-60] Even nephrectomy did not halt the appearance of hypertension, according to one report, suggesting that it is not dependent upon a renal mechanism for its maintenance.[61] Elevation of blood pressure occurred no matter whether the hormone was injected in the acetate form or given as subcutaneous pellets; however, Green[62] reported no hypertension if intrasplenic pellets were implanted and suggested inactivation by the liver. There is only one study, that of Summers,[63] in which the results were contrary to those generally obtained.

Morphological changes caused by massive doses of desoxycorticosterone acetate and salt were first described by Selye and his co-workers.[55, 64] These included the development, in several animal species, of a decrease in adrenal size, and in later studies of cardiac hypertrophy and widespread vascular lesions–similar to those seen in human nephrosclerosis and in the accelerated phases of essential hypertension. Subsequent studies by Knowlton and her associates,[65] employing much lower dosages in rats, revealed no significant vascular lesions but some degree of cardiac and renal enlargement (even in the absence of hypertension).

In addition, a change in renal histology was produced by the desoxycorticosterone acetate, consisting of distention of cortical and medullary tubules, swelling and vacuolization, and sometimes atrophic changes in the convoluted tubules. With these smaller doses, striking hypertension appeared within a matter of a few weeks only in nephritic rats given the steroid (the nephritis having been induced by a cytotoxic serum), but it was not evident in controls. Incidentally, in the dosages employed, adrenal cortical extract did not produce hypertension in normal or nephritic rats,[48, 65]

Selye[66] noted that the degree of pathological response to desoxycorticosterone acetate was intensified by an increase in the sodium chloride supplement in the diet or by preliminary excision of one kidney; similarly, the group working with Knowlton[67] found that the action of the steroid was potentiated by salt. Still other workers reported that desoxycorticosterone, particularly in the presence of added sodium salts, resulted in an impaired renal function as measured by clearance techniques.[59, 68] The adrenal cortex of rats injected with this compound presented atrophic changes in the subcapsular zone but only when the animals were maintained on a liberal intake of salt;[67] and under similar conditions a decrease in adrenal size was confirmed by Carnes and his associates.[69] "Whatever may be the mechanism responsible for the various changes induced by desoxycorticosterone acetate, it is obvious that they are dependent upon a liberal supply of the sodium ion in the diet."[67]

The water and electrolyte changes which follow the administration of desoxycorticosterone esters in small or large doses constitute a familiar but separate story. The apparent lack of relationship of salt and fluid retention to the appearance of hypertension will be brought out later. It has been shown that potassium chloride tends to correct the depression of potassium in the serum and the intracellular replacement of potassium by sodium but has no effect upon the hypertension in nephritic animals nor upon the anatomical lesions.[67] Green[60, 70] observed the increased voluntary fluid intake of rats receiving the steroid; merely because the intensity of the blood pressure rise could be related to fluid exchange, despite some evidence to the contrary, he suggested that hypertension might be a compensatory mechanism to fluid and electrolyte changes. Selye[66] has claimed that the concurrent administration of ammonium chloride tends to inhibit the development of vascular and renal

damage, but then it must be recalled that massive doses of desoxycorticosterone were generally employed in his studies. Raising the question of some action on peripheral vascular tone, it has been stated that desoxycorticosterone protects dogs against the depressor effect of intravenous hypertonic sodium chloride.[71] A final comment—no direct relationship of hypertension to the urinary output of antidiuretic factor, increased by desoxycorticosterone, was established.[72]

Observations in Man

As might be expected, the first attempts to relate the adrenal cortex to hypertensive vascular disease in man were morphological. The elevated blood pressure of some patients with hyperfunction of the adrenals, either cortical or medullary, has already received comment. The nodular hyperplasia of the medulla reported by Goldzieher,[73] and the "sympathogenic neurohormonal" emphasis of Raab,[74] need not be discussed here except to remind us that epinephrine-like compounds and sympathetic nerve activity may possibly modify steroid elaboration.

There are numerous references to *adenomatous or nodular hyperplasia* of the adrenal cortex in essential hypertension since the description in 1904 of adrenal enlargement and increased cortical lipoid in patients with contracted kidneys.[75] Many authors observed increased adrenal weight, hyperplasia, adenomata or nodules with increased frequency in hypertensive subjects.[76-84] Others, on the other hand, felt that these abnormalities were uncommon or existed with equal frequency in normotensives.[85-88] *Hypertrophy of the adrenal veins* was mentioned by several investigators,[89,90] but this finding could not be confirmed in subsequent studies.[85] If all these pathological reports were laid end to end, it would be apparent at best that anatomical changes occur with slightly greater frequency in patients with an elevated blood pressure, and that such changes are evident in only a small percentage. It is, therefore, highly doubtful that any significance can be attached to these morphological findings alone.

In 1939, Loeb and his associates[91] called attention to two patients whose arterial pressure exceeded normal limits in the course of *treatment of Addison's disease with desoxycorticosterone esters*. Since that time these observations have been confirmed and extended.[92-102] At the Presbyterian Hospital, together with Drs. Knowlton, Lowell and Loeb,[100] we observed the appearance of hypertension in a number of patients

with Addison's disease in the course of prolonged administration of desoxycorticosterone acetate in therapeutic doses. The slow increase in blood pressure could not be correlated with abnormal retention of the sodium ion nor with an increase in circulating blood volume. It was not dependent apparently upon an abnormally labile peripheral vascular system as measured by the cold pressor test. In our clinic today, the majority of patients with adrenal cortical insufficiency exhibit some elevation of arterial tension, providing they are receiving adequate therapy with this steroid given parenterally or in the form of subcutaneous pellets. One individual has developed transitory retinal hemorrhages; another has sustained, coincidentally or otherwise, a myocardial infarction after several years of drug-induced hypertension.

Desoxycorticosterone acetate, administered to three normotensive patients without adrenal disease, was associated with a gradual increase in blood pressure over a period of weeks without more than transient salt or water retention.[100] As in the Addisonian group, the blood pressure returned to normal values as soon as the drug was withdrawn. One of these patients, toward the close of the experimental period, complained of severe headaches, with the appearance of a subconjunctival hemorrhage and a rise in pressure to 160/108 during the final week.

The blood pressure *response of hypertensive individuals to desoxycorticosterone acetate* was next considered. In a study undertaken with Dr. David Blood,[103] utilizing "resting" blood pressure measurements in patients on a constant regimen, this steroid (10 mgs. daily for a week) caused no significant change in the arterial tension of 10 normotensive subjects, whereas definite increases in systolic and diastolic readings were obtained within a few days in 14 patients with uncomplicated hypertensive vascular disease. The prompt rise in blood pressure in those with hypertension could not be ascribed to changes in salt and water retention alone as there were comparable transitory changes in the normotensive group. Alterations in cardiac output were not responsible for this pressor effect.

Daily injections with this steroid for longer periods produced a transient or at times a sustained increase in the "resting" blood pressure of hypertensive patients.[104] The continued treatment was associated with a progressive drop in serum potassium concentration, an increase in carbon dioxide content, and a fall in chloride concentration. Salt and water retention, on the other hand, was observed only during the first

seven to ten days of treatment, with reversal to control levels thereafter. Although Goldman and Schroeder[105-106] recorded an immediate pressor effect after the intravenous injection of desoxycorticosterone acetate, we were unable to reproduce this action using the glucoside. In our clinical studies the fact that the pressor response occurred in a matter of days rather than of hours was testimony against a direct humoral mechanism.

At this point it might be appropriate to tell the story of a patient with documented essential hypertension who subsequently developed hypoadrenalism.[107] After it was established that he had Addison's disease, this man showed a persistent elevation of blood pressure while under treatment with desoxycorticosterone for a matter of years. Thereafter, replacement therapy with salt alone, even though the patient was maintained in water and electrolyte balance, resulted in a drop in blood pressure to normal limits. One could not help but conclude that the adrenal cortex or appropriate steroid substitution therapy was important for the development or maintenance of this man's essential hypertension.

As in the animal studies, *sodium metabolism* also enters the human story. The effect of rigid sodium chloride restriction in hypertensive vascular disease has been reviewed elsewhere.[108] In our opinion there is convincing evidence that the disorder is associated with a disturbance of salt and water metabolism, and that some modification of the "resting" blood pressure (of still doubtful therapeutic application) may result from extremes of sodium withdrawal or supplementation. It is claimed that serum sodium-to-chloride ratios are elevated in proportion to the height of the diastolic pressure in hypertensives.[109] Furthermore, despite an otherwise constant regimen, sodium restriction is generally followed by immediate significant weight loss and increased urine output in control subjects which are not evident in hypertensive patients.[110] And lastly, in our clinic, Dr. Kermit Pines has noted that treatment with thiocyanates increases the excretion of sodium in some cases; perhaps its occasional depressor action operates through the same channels as salt restriction. These observations are consistent with, but certainly not proof of the view that the adrenal cortex may be implicated. Of perhaps greater pertinence is the fact that rigid restriction of sodium chloride masks the pressor response of hypertensives to desoxycorticosterone.[111, 112]

Preliminary trials with *other adrenal steroid preparations* have been undertaken with the view that depression of existing adrenal cortical function or counteraction of some desoxycorticosterone-like pressor hormone might alter the blood pressure. Although adrenal cortical extracts exerted no immediate blood pressure effects,[106] we were able to demonstrate a small decrease in "resting" values in three of four uncomplicated hypertensive subjects following the continued administration of such an extract for one month.[113] The changes in arterial tension could not be ascribed to alterations in serum volume, fluid or electrolytes, or apparent change in cardiac action. Furthermore, the simultaneous use of adrenal cortical extract appeared to block the pressor effect of desoxycorticosterone acetate.[114] Finally, and all of these studies were carried out in association with Dr. Pines and others, opportunity was given us to employ *cortisone* in the acetate form prepared synthetically (Merck).[115] Administered in doses of 80 mgs. daily, small but definite decreases in "resting" blood pressures have now been recorded in four hypertensive patients. The decline usually occurred immediately after the discontinuance of therapy in these short-term studies. In another hypertensive patient, treated for a month with 200 mgs. of cortisone, a preliminary rise in arterial tension was followed by a more pronounced and sustained fall. In contrast, and similar to Guadino's adrenalectomized animals,[17] the blood pressure rose in a patient with Addison's disease more than would be expected on the basis of salt and water retention alone. This suggests that this steroid requires the presence of an intact adrenal for its depressor action and may be pressor in the absence of the adrenals. Cortisone, in our experience, exerts little effect on the blood pressure of normotensive man.

We have confirmed the report of Hench and his associates[116a] that *adrenocorticotropic hormone* (Armour) may raise the blood pressure of non-hypertensive patients. In addition, a marked increase in arterial tension and signs and symptoms of hypertensive encephalopathy followed its use in one of several hypertensives.[116b] Dosage and plasma volume changes played little part in this effect and it was not due to an increase in circulating epinephrine or nor-epinephrine. Cardiac output changes occurred but were variable. Further hemodynamic study of this drug is needed. At any rate, the adrenocorticotropic hormone—known to produce adrenal cortical hypertrophy—does not lower the blood pressure.

A possible relationship of the adrenal cortex brought forth many therapeutic attempts to modify the hypertensive state. Beneficial results were claimed after *irradiation of the adrenals*,[117-120] *denervation or subtotal bilateral adrenalectomy*.[121-126] It would be of interest to repeat these inconclusive studies in light of modern concepts of adequate baselines and consideration of psychotherapeutic factors in evaluating results. Dramatic effects following *complete bilateral adrenalectomy*, in a woman with severe hypertension and diabetes, have recently been reported by Green and his associates.[127] The final results of this and comparable studies must be awaited with interest.

Can hypertension be maintained or can it appear in man in the absence of intact adrenals? Apparently the answer is yes. We have repeatedly observed the persistence of an elevated blood pressure in some hypertensive patients who developed chromophobe adenomata of the pituitary with laboratory evidence of secondary hypoadrenalism. Loeb[96] has commented on the Addisonian subject whose blood pressure rose to 160/100 when salt was given in doses of 15 gms. daily without any cortical hormone; at autopsy this patient was found to have marked renal arteriolosclerosis and both adrenal glands were replaced by tuberculous masses. In addition, there is a case report including pathological findings of another individual with Addison's disease, hypertension becoming apparent even in crisis in association with bilateral cortical infarction of the kidneys.[128] Furthermore, toxemia of pregnancy and hypertension have developed in women with Addison's disease, the blood pressure elevation continuing even after the withdrawal of steroid therapy.[129] The mechanism of these forms of hypertension would seem to exclude a primary role of the adrenal gland, but these observations do not apply necessarily to the situation in essential hypertension.

Even though the behavior or reactivity to certain steroids is apparently different, the final question may be asked: *is there any evidence of adrenocortical dysfunction* in hypertensive vascular disease? Increased sensitivity of hypertensives to small doses of methacholine has been reported,[130] a situation encountered also in Addison's disease.[131] A small decrease in the excretion of urinary 17-ketosteroids has been noted by some observers.[88, 109] Fisher and Hewer[83] have recorded an increased adrenal content of sudanophil and anisotropic lipids. Dobriner's group[132] isolated a steroid, found in the urine of some hypertensives, but only rarely in other conditions.

On the other hand, determinations of the formaldehydogenic steroid content of hypertensive urine have been within the normal range.[133, 134] and Tobian and Joseph[134] have disclosed no differences in plasma corticoids. These latter workers reported a slightly lower fasting blood eosinophil concentration, and in this connection the few observations of Laragh and Almy[135] should be mentioned—an exaggerated drop in circulating eosinophils following epinephrine or insulin injection in hypertensive subjects.

At the present time, therefore, evidence of adrenal dysfunction in essential hypertension remains to be established; but then, it is possible that blood pressure regulation, perhaps in some way concerned with salt and water metabolism, represents a fairly discrete function independent of other known actions of the adrenal cortex.

Comment

A conspicuous feature of this review is the large number of references that have already accumulated which bear on an adrenal cortical relationship in hypertensive states. It is equally conspicuous that the adrenal seems to be connected in some fashion with many forms of experimental hypertension as well as the various approaches being made in different etiological directions. It is most conspicuous, however, that we remain completely in the dark as far as possible mechanisms are concerned.

The weight of evidence would indicate that the adrenal cortex and the sodium ion are definitely related in some way to the regulation of blood pressure and that a possible relationship to essential hypertension cannot as yet be excluded. Whether primary or secondary mechanisms are involved remains completely obscure, but no data have been presented thus far which establish the adrenal cortex as playing a primary causative role in hypertensive disease in man. In fact, the delays and lags in steroidal response are good testimony pointing toward complex mediation as opposed to some primary humoral action.

Is the adrenal merely the "guardian of the glomerular filtrate?"[83] Should attention be paid to Heinbecker's speculation[136] referring to a humoral mechanism operating through the hypothalamic nuclei and the neurohypophysis, or to Selye's "diseases of adaptation?"[66] Do the steroids achieve their effects through modification of the pituitary release of adrenocorticotropic hormone?[137] Do products of the adrenal

serve to alter the reactivity of vessels or the sensitivity of smooth muscle to other pressor and depressor agents?[12] Is it remotely conceivable that an excess of a pressor hormone or a deficiency of a depressor hormone exists in the hypertensive state, that the adrenal cortex may possess a homeostatic group of substances concerned with blood pressure regulation?[113, 138] There is at present no definitive answer to these questions.

We really know very little about the peripheral action of the steroid hormones. The problem would be greatly simplified if there were readily-available methods for measuring desoxycorticosterone-like substances in the circulation. The long-range therapeutic effectiveness of complete ablation of the adrenals remains to be determined. Only through such information can the answers to these and other questions be provided.

It is doubtful that the solution to the problem of hypertensive vascular disease lies within the adrenal. On the other hand, one should hesitate to discard this possibility as completely unprofitable, for it is quite conceivable that an understanding of adrenal mechanisms may cast light on some fundamental mechanisms of hypertensive disorders. Meanwhile, to quote Dr. Joseph Jailer, the adrenal cortex may be the "stockpile of the steroids," but it remains to be seen whether these structures represent the "seat of the soul."

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The New York Tuberculosis and Health Association announces that a fellowship will be available from July 1, 1950 to June 30, 1951. The fellowship is designed to support a qualified medical investigator who will devote full time to a research project with a definite bearing on tuberculosis. Assurance must be provided that the applicant will be acceptable in the laboratory or clinic of his choice and that he will be provided with the facilities necessary for the pursuit of the work. It is preferred that such laboratory or clinic be located in New York City.

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CARDIAC CATHETERIZATION IN THE DIAGNOSIS OF CONGENITAL HEART DISEASE*

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UNTIL recently, congenital heart disease has been largely of academic interest to physicians. Recent developments in cardiac surgery have followed closely upon improvements in thoracic surgery and anesthesia. As new operations on or around the heart have been devised during the last decade, the onus of a correct pre-operative diagnosis has fallen onto the shoulders of the internist. Before the advent of angiocardiography and cardiac catheterization, a correct diagnosis of many congenital heart lesions had to await autopsy examination. Inability to be sure of the correct diagnosis during life made for slow progress in our knowledge of these disorders. Increasing familiarity with the various congenital heart malformations correctly diagnosed during life now makes it possible to study a given abnormality in a detailed manner so that by the usual approach of history, physical examination, fluoroscopy of the heart, and electrocardiogram, a correct diagnosis can usually be made without resorting to more complicated procedures.

In acquired heart disease, it is usually stated that 60 per cent of all information to be obtained is derived from a careful history, 25 per cent from physical examination and 15 per cent from laboratory procedures (x-ray and electrocardiogram). In congenital heart disease, just the opposite is true. About 15 per cent of the information comes from history, 25 per cent from physical examination, and 60 per cent from laboratory procedures. The history may date from birth or childhood, tells us the extent of physical incapacity, may tell us if the patient has been cyanotic. A history of cyanosis may be quite misleading, however, because after one or two physicians have made inquiries on this point,

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the answer becomes almost uniformly positive, whether or not cyanosis really exists. Physical examination reveals the presence of a murmur which has obviously not been acquired and must therefore be congenital, but unlike many acquired murmurs is not diagnostic except in the case of patent ductus arteriosus. Fluoroscopy of the heart reveals abnormalities of contour and the size of some of the chambers. I should like to emphasize, however, with all apologies to any radiologists who may be present, that in our experience x-ray and fluoroscopy are not reliable in evaluating the size of the right auricle, *are* quite reliable as regards the left auricle, and are good in recognizing ventricular enlargement but are not always correct in identifying which ventricle is enlarged. We have found the electrocardiogram to be the more reliable in identifying which ventricle is hypertrophied. Further information to be derived from the x-ray is the size of the pulmonary artery and the prominence of the pulmonary vascular markings at the hilar regions of the lung. These markings are regularly increased when pressure in or flow of blood through the pulmonary artery is increased and, with one exception to be discussed, are of normal or decreased prominence when pressure and flow are normal or decreased. If, with evaluation by these methods, the diagnosis is still uncertain, angiocardiography, which will be discussed by Dr. Morgan, and cardiac catheterization[1] will usually reveal the important lesions present.

Before one can make a correct morphological diagnosis, two principles must be recognized. The physician must first have some idea of the differential diagnostic possibilities and secondly, in the case of congenital heart disease, some concept of the physiological disturbances created by the lesion, since the abnormal flows and pressures produce changes in the contour and size of the heart and pulmonary vessels from which logical deductions concerning the underlying lesions can usually be made.

Under the age of, say, five, congenital heart disease is extremely complicated. It is in this age group that the greatest challenge exists. During this period, the serious lesions and the multiple lesions are lethal. The simpler lesions compatible with life are prone *not* to have distinctive patterns. Above the age of about five, most of the patients with seriously malformed hearts have expired, leaving a relatively few major types with which we, as physicians, are confronted. The majority fall into the following groups: simple pulmonic stenosis, tetralogy of

Fallot, Eisenmenger's complex, atrial septal defect, ventricular septal defect, and patent ductus arteriosus. Less frequently seen are tricuspid atresia, anomalous pulmonary veins emptying into the right atrium, levoposition of the pulmonary artery, transposition of the great vessels, aortic septal defect, and a variety of other lesions. Although coarctation of the aorta is fairly common, it will not be discussed here because cardiac catheterization does not serve any useful diagnostic purpose.

In the discussion that follows, emphasis will be placed on the physiological changes that occur and their influence on the x-ray and electrocardiogram. Only by this approach have we been able to improve our clinical recognition of the various disorders and thus to abandon the use of the cardiac catheter in many cases. It is now reserved for those cases which are not distinctive.

Technique of cardiac catheterization: The cardiac catheter is a modified ureteral catheter with a curved tip. It is sufficiently stiff so that rotation of one end turns the curved tip at the other end. Due to its radiopacity, it may be guided to the desired position under fluoroscopic observation. The median basilic vein is the usual site of introduction. In infants, the jugular or the femoral vein has been used. In the older age group, novocaine is used for anesthesia. In the younger age group, a general anesthetic must be employed. The vein is exposed and the catheter introduced. It is guided fluoroscopically into the subclavian vein, superior vena cava, right auricle, right ventricle, and pulmonary artery. If it is allowed to obstruct the pulmonary artery, it is in direct connection with the pulmonary capillary bed so that blood samples so obtained are arterial instead of venous and the pressure so measured is within a millimeter or so of the true pulmonary capillary pressure.[2] Pressures can be recorded through the catheter and blood samples withdrawn and analyzed for their content of oxygen. In congenital heart disease, left-to-right shunts through defects in the cardiac septa will be characterized by the appearance of arterial (highly oxygenated) blood in the corresponding chamber in the right side of the heart.

Normal variations: Figure 1 shows characteristic pressure tracings in a normal patient. It will be observed that except that the pressure in the pulmonary artery is quite low, the contour is the same as in a systemic artery with a systolic rise, a dicrotic notch due to closure of the pulmonary valve, and a fall to the diastolic level just before the next ventricular systole. The systolic pressure in the right ventricle is iden-

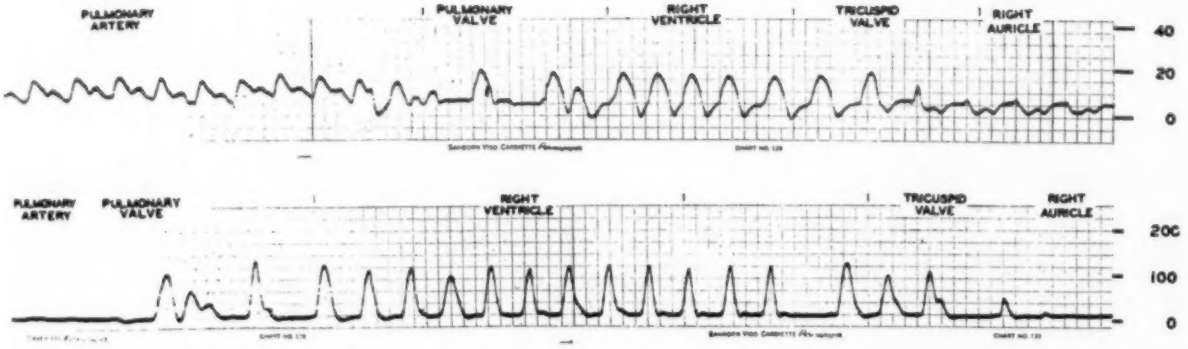

Figure 1—Pressure tracings obtained through a catheter during continuous withdrawal of the catheter from pulmonary artery through right ventricle and into right auricle.

Upper curve: Normal patient. Note that the systolic pressure in the right ventricle is the same as that in the pulmonary artery.

Lower curve: Patient with pulmonic stenosis. Note that the systolic pressure in the right ventricle is higher than that in the pulmonary artery.

tical with that in the pulmonary artery. The diastolic pressure in the ventricle is the same as the pressure at the same time in the right auricle.

Blood samples withdrawn from the different chambers in the lesser circulation normally vary somewhat in their oxygen content. Blood entering the right auricle comes from the superior vena cava, inferior vena cava, and coronary sinus. The amount of oxygen in these different venous bloods varies greatly so that a considerable variation in oxygen content is encountered in different parts of the right auricle. Less variation occurs in the right ventricle and by the time blood has reached the pulmonary artery, the oxygen content is remarkably uniform. Variations in the oxygen content in the various chambers have been described in detail.[3] Because of these normal variations, two or more samples of blood must be withdrawn from each chamber in order to recognize with any degree of certainty an abnormality when it exists.

Pulmonic Stenosis: The commonest example of pulmonic stenosis is the tetralogy of Fallot. Simple pulmonic stenosis without other accompanying defect has always been considered a rarity. It has turned out, however, to be one of the common congenital cardiac lesions[4,5,6] and has usually been diagnosed clinically as ventricular septal defect.

A. *Simple pulmonic stenosis* is characterized clinically by the absence of cyanosis, a systolic murmur of varying intensity in the 2nd, 3rd, or 4th left intercostal space, and right ventricular hypertrophy or right bundle branch block by electrocardiogram. X-ray and fluoroscopy of the heart may or may not show right ventricular enlargement, but in almost all cases there is *prominence of the pulmonary artery accompanied by normal or decreased pulmonary vascular markings* because pressures and blood flow through the lung are normal or reduced. The cause of the enlarged pulmonary artery has been discussed for over one hundred years and no reasonable explanation has yet been given. The combination of the murmur, electrocardiographic and x-ray findings are practically pathognomonic. By cardiac catheterization the diagnosis is made by pressure recording alone. Instead of finding identical systolic pressures in the pulmonary artery and right ventricle, this pressure is higher in the right ventricle than in the pulmonary artery, indicating an obstruction between the two, i.e., pulmonic stenosis (Figure 1).

B. *The tetralogy of Fallot* consists of pulmonic stenosis accompanied by a ventricular septal defect, an aorta which straddles both ventricles (dextroposition of the aorta) and right ventricular hypertrophy. Blood

enters the right auricle and goes to the right ventricle. Due to the obstruction to outflow through the pulmonary valve, there is a diminished blood flow into the pulmonary artery and lung, and a shunting of blood into the systemic circuit producing cyanosis. Since the right ventricle is in direct connection with the aorta, the systolic pressures in the right ventricle and in the aorta are identical. The path taken by the cardiac catheter may be from right ventricle through the stenotic pulmonary valve and into the pulmonary artery. Under these circumstances, pulmonic stenosis will be recognized by the higher systolic pressure in the right ventricle than in the pulmonary artery, dextroposition by identical systolic pressures in the right ventricle and brachial artery, and a right to left shunt by arterial oxygen unsaturation. In some cases, the catheter cannot be introduced into the pulmonary artery. Instead, it passes from the right ventricle directly into the aorta. Under these circumstances, dextroposition of the aorta is recognized by finding identical systolic pressures in the aorta and right ventricle, a right-to-left shunt by arterial oxygen unsaturation, but pulmonic stenosis cannot be demonstrated. One must depend on the appearance of the pulmonary artery and pulmonary vascular markings on the x-ray film. In the tetralogy of Fallot, the pulmonary artery and hilar vascular markings are classically diminished whereas if pulmonic stenosis is not present (Eisenmenger's complex) these are both greatly accentuated. The salient findings in a patient in whom the cardiac catheter was introduced into the pulmonary artery as well as into the aorta were as follows:

Source of Blood	*Pressures mm.Hg*	*Oxygen Content cc/l*
Aorta	105/73	204 (69 per cent)
Pulmonary Artery	7	150
Right Ventricle	105/7	—

Eisenmenger's complex: This condition has the same anatomical defects as the tetralogy of Fallot with the exception that pulmonic stenosis is absent. The septal defect varies in size and as it approaches complete absence, this condition merges imperceptibly with the anatomical condition known as cor triloculare biatriatum, i.e., two atria and a common ventricle. Although usually the two ventricles are anatomically partially separated by a septum, physiologically they are

common chambers with identical pressures because of the over-riding aorta. Cyanosis develops late, there is a pulmonic systolic murmur, the electrocardiogram shows right ventricular hypertrophy, and the x-ray reveals an enlarged right ventricle, large pulmonary artery, and prominent pulmonary vascular markings. The systolic pressures in the aorta (or brachial artery) and right ventricle are identical (because of aortic dextroposition) as are those in the right ventricle and pulmonary artery (because there is no pulmonic stenosis). Actually there is a "stenosis" in the arterioles of the lung. The pulmonary "capillary" pressure is normal, the pulmonary arterial pressure is aortic in its magnitude, and the pulmonary arteriolar resistance approximates that in the systemic circuit, i.e., it may be 15 to 40 times the normal pulmonary resistance. This high resistance produces an effective "stenosis" as in the tetralogy of Fallot, but it is located in the pulmonary arterioles instead of at the pulmonary valve. The net result is minimal shunting of blood either from left-to-right or right-to-left. The late right-to-left shunt that occurs in these individuals is probably due to a pathological increase in the pulmonary resistance which eventually becomes higher than that in the systemic circuit. Curiously enough, history, physical examination, electrocardiogram, x-ray, and fluoroscopy cannot usually differentiate with any degree of certainty this condition from atrial septal defect. Venous catheterization is diagnostic in Eisenmenger's complex by finding identical systolic pressures in the brachial artery, right ventricle, and pulmonary artery. The following is an example:

Site	*Pressure mm.Hg*
Pulmonary Artery	117/56
Brachial Artery	116/72
Right Ventricle	117/1
Pulmonary "Capillary"	12

Atrial septal defect: Defects may occur in the septum separating the two atria. Whether this defect is a patent foramen ovale or persistent ostium primum or secundum is not revealed by the venous catheter. In any event, there is a large shunt of blood from left atrium to right atrium and from here blood passes through the right ventricle, pulmonary artery, lung, and back again to the left atrium. These indi-

viduals have the largest shunts of blood that we have encountered. Late in the course of the disorder, changes occur in the pulmonary vasculature so that resistance to flow through the arterioles of the lungs becomes high and pressure in the pulmonary artery becomes greatly elevated. The right ventricle, the pulmonary artery, and the pulmonary vascular markings attain great prominence by x-ray. These findings coupled with a similar history, physical examination, and electrocardiogram make its differentiation from Eisenmenger's complex difficult. When the cardiac catheter is introduced into the right auricle, it may sometimes be introduced through the defect into the left atrium and even out into a pulmonary vein. The latter experience makes it difficult to differentiate atrial septal defect from an anomalous pulmonary vein emptying into the right auricle. Arterialized (highly oxygenated) blood is found in the right auricle as compared with the superior vena cava as shown by the following example:

Source of Blood	*Oxygen Content cc/liter*
Superior Vena Cava	159
Right Auricle	203
Right Ventricle	209
Pulmonary Artery	209

Ventricular Septal Defect (Roger's disease): Pathological reports have usually shown ventricular septal defect to be much less common than the other congenital abnormalities under discussion. This has likewise been our own experience. These individuals are not cyanotic and they have a pulmonic systolic murmur which is not distinguishable from that of pulmonic stenosis, atrial septal defect, and Eisenmenger's complex. Both ventricles are called upon to perform increased work so that by x-ray there is prone to be a non-specific cardiac enlargement, and the electrocardiogram shows little or no preponderance of either ventricle. Another condition which may produce similar findings and lead to an erroneous diagnosis is pulmonic stenosis with an associated aortic septal defect, i.e., a communication between the aorta and pulmonary artery just beyond the sites of the aortic and pulmonary valves. Cardiac catheterization reveals a significantly higher oxygen content of blood in the right ventricle than in the right atrium:

Source of Blood	*Oxygen Content cc/liter*
Right Atrium	125
Right Ventricle	156
Pulmonary Artery	156

Patent Ductus Arteriosus: Little need be said concerning this disorder, since it is assumed that all are familiar with the typical machinery murmur. On cardiac catheterization, oxygenated blood is found in the pulmonary artery as compared with values found in the right ventricle:

Source of Blood	*Oxygen Content cc/liter*
Pulmonary Artery	137
Right Ventricle	103
Right Auricle	102

Summary and Conclusions

In conclusion, cardiac catheterization in the diagnosis of congenital heart disease might at present be evaluated as follows:

1. It is diagnostic in the tetralogy of Fallot, Eisenmenger's complex, and uncomplicated pulmonic stenosis.

2. Although patent ductus arteriosus, ventricular septal defect, and atrial septal defect may usually be detected with ease by cardiac catheterization, small defects are easily overlooked. Much depends on the skill of the catheter-passer in inserting the catheter through the defect or in placing the tip of the catheter in the stream of arterial blood that is being shunted from left to right.

3. Cardiac catheterization gives confusing or inadequate data for interpretation when there are multiple defects such as in the case of the coexistence of atrial and ventricular septal defects together with a patent ductus arteriosus. Another example is that of tricuspid atresia with its accompanying atrial septal defect and ventricular septal defect or patent ductus arteriosus. In this case, the only abnormality revealed is atrial septal defect.

4. Small defects in the septa are easily missed. The size and precise location of a defect in a given septum, which is of crying interest to

the cardiac surgeon, is not revealed except in a very general way by cardiac catheterization. It is not possible to detect aberrant coronary arteries, bicuspid pulmonic valves, or anatomical abnormalities confined to the left side of the heart.

5. It should be remembered that this is a physiological method from which certain structural abnormalities can justifiably be deduced, just as angiocardiography, which Dr. Morgan is to discuss, is essentially an anatomical method from which many physiological abnormalities may be deduced. There are limits beyond which interpretation of the findings by cardiac catheterization is not justified. In order to arrive at a correct diagnosis, interpretation should be coupled with all of the other clinical and laboratory data that are available.

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PRESENT METHODS IN THE DIAGNOSIS OF HEMOLYTIC DISORDERS*

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I AM grateful for the invitation of the Academy to deliver the Carpenter Lecture this evening, and for the opportunity to discuss with you the problem of diagnosis of the hemolytic disorders. I shall attempt to survey the various features which I consider of principal significance and in so doing I hope I shall not give undue emphasis to the hepatic and pigmentary aspects, in which I have had relatively more interest. The most logical sequence, perhaps, is to commence at the bedside and proceed later to the laboratory.

The history of anemia with or without chronic or intermittent jaundice, or of enlargement of the spleen, and the presence of any of these features amongst other members of the family, are points of obvious importance. The statement that other members of the family have suffered from "pernicious anemia" should not be accepted at face value, as in our experience this has often been confused in the past with familial hemolytic anemia.

The relation of various chemicals to hemolytic anemia is well known, so that occupational or accidental exposure, especially in cases of acute anemia, should be carefully inquired into.

Fever, chills, abdominal distress, and joint pain, are symptoms that may occur both in the crises of chronic hemolytic anemia, whether familial or acquired, and of course, in that great masquerader, sickle cell anemia. In fact, joint pain is rare in hemolytic disease, except in the latter form.

Let me emphasize that there is the widest variation in the degree of jaundice and anemia. They are by no means correlated; in fact, there is generally a somewhat inverse correlation in that the patients with the

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most jaundice are likely to be the least anemic, and vice versa. The so-called hemolytic "crises" constitute an exception, however, in that during these periods jaundice and anemia may increase together.

I mention splenic enlargement only to emphasize that there are well-defined cases of severe hemolytic anemia in which the spleen is not palpable at any time. We have studied several instances in which, despite all efforts on many occasions, the spleen was not felt but at the time of operation weighed as much as 450 grams. In some instances, the roentgenologist may be of considerable aid in demonstrating an enlarged spleen that is not palpable nor demonstrable by percussion.

The liver is often enlarged and even tender in acute hemolytic crises regardless of their cause. Mild enlargement of the liver is common in chronic hemolytic anemia, but any considerable enlargement or evidence of hardening always raises the question as to whether the hemolytic anemia is secondary to a diffuse disease of the liver, such as cirrhosis. I would emphasize now that macrocytic hemolytic anemia is at times outspoken in cases of cirrhosis of the liver.

Lymphadenopathy may be touched upon briefly only because of the occurrence of macrocytic hemolytic anemia in association either with Hodgkin's disease or leukemia.

Chronic leg ulcers are much more frequently associated with sickle cell anemia than with any other form of hemolytic disorder, but they may be encountered in chronic familial hemolytic jaundice.

In the laboratory, the blood deserves primary attention. The importance of studying the size and shape of the red cells is only too well known. Determination of the mean cell diameter is often of decisive value. The most elegant and informative technique of course, is the Price-Jones curve, but unfortunately this is time-consuming and not easily adaptable to routine usage. The halometric method is simple and quick, but not as accurate. Nevertheless, in the hands of the same practiced technician, it yields very helpful information. The most important thing to determine is whether the red cells on the average are larger or smaller than the normal. The halometer usually provides this information. The practicing physician may obtain the same information by another simple method; namely, the superimposition of cells from a normal individual upon a stained smear of the patient's cells. Both smears, of course, must be very thin in order that the unstained normal cells and the stained patient's cells will, for the most part, occupy sep-

arate areas. In this way, a direct comparison may be made, and it is usually easy to tell whether the patient's cells on the average are larger or smaller than the normal. No originality is claimed for this method, as superimposition, by one means or another, has been repeatedly used in the past.

In cases of outspoken spheroidocytic anemia, it is generally possible to tell at once that the mean cell diameter is reduced; the highly characteristic deeply staining microcytes easily stand out.

A further characteristic of spheroidocytic hemolytic anemia is the increase or relative increase in the mean cell volume, due to increased thickness of the cells. Thus, from the standpoint of volume these anemias are macrocytic or normocytic, but from the standpoint of diameter, they are microcytic. This lack of correlation itself is at once indicative of the presence of spheroidocytosis. In the following the terms macrocytic, normocytic, and microcytic are based upon the mean cell diameter rather than the mean cell volume.

Evidences of increased erythropoietic activity are found in most hemolytic disorders. The reticulocyte count is significantly elevated in more than 90 per cent of the cases. I shall emphasize certain exceptional instances a little later. In toxic hemolytic anemias, such as those due to chemical or heavy metal poisoning, basophilic stippling is often prominent, while it is usually not increased in the hemolytic disorders of other etiology. It might be supposed that normoblasts or other nucleated red blood cells would characteristically be found in considerable number in the peripheral blood in hemolytic disease. Yet, as a rule, normoblasts are absent or rare. This is of interest from a fundamental standpoint since it reveals that the release mechanism from the bone marrow is usually well preserved even though the regenerative activity is greatly increased. The reticulocytes may be 50 per cent or higher with but rare normoblasts in the peripheral blood, even though the bone marrow is markedly hyperplastic-normoblastic. However, there are atypical hemolytic states in which normoblasts may appear in considerable number.

Decreased osmotic resistance of the erythrocytes is closely correlated with the presence of spheroidocytosis. If the erythrocyte measurements and the morphology of the red cells in the stained smear clearly indicate a spheroidocytic anemia as discussed above, the fragility test becomes almost superfluous and is really only necessary for con-

firmation in doubtful cases. It should be emphasized that there are many examples of macrocytic or normocytic hemolytic anemia without any demonstrable change is osmotic fragility of the red cells. Before leaving the subject of spheroidocytosis and increased fragility, it should be emphasized that these phenomena are not restricted in occurrence to familial or congenital hemolytic anemia, but may be encountered in hemolytic anemias secondary to infectious or chemical agents.[1]

An increased titer of cold agglutinins is often present to a striking degree in hemolytic anemia, especially of the macrocytic or acquired type. If this is at all marked the practicing physician can easily recognize it at the bedside. On cooling a small oxalated blood sample below body temperature, the blood is seen to become sand-like. If it is then warmed again, it smoothes out. This test can be carried out to good advantage simply with a hot and cold water faucet. It should be noted that cold agglutinins may be encountered in markedly increased titer in certain other diseases without hemolytic anemia, as for example, atypical or virus pneumonia. Although it is unlikely that the cold agglutinins themselves are often directly implicated in the genesis of the hemolytic disease, they are commonly encountered in patients with hemolytic anemia who have transfusion reactions of unknown mechanism. It seems likely that cold agglutinins are often accompanied by other abnormal substances operative at body temperature.

The Coombs' test for blocking antibodies is one of the more important recent advances in the study of hemolytic disorders.[2, 3, 4] Described very briefly, this depends upon the use of an anti-human globulin serum brought in contact with the red blood cells of the patient under study. The serum has been prepared previously by immunizing a rabbit against human globulin. This anti-serum is now marketed. The available information about the test is by no means adequate, but it has become clear that it is commonly positive in acquired hemolytic anemias of various etiology.[3, 4, 5] It is evident that in these conditions the red cells have a hyper-immune globulin adsorbed on their surface. Although this so-called blocking antibody is probably combined with a specific antigen, clumping of the red cells has not occurred, but is rapidly produced when they are mixed with the anti-human globulin serum. This test is very easy to carry out, and has become of much practical value. It is rather uniformly positive in hemolytic anemias due to Rh sensitivity,[2, 3] also in certain idiopathic acquired hemolytic anemias. It appears that

it may occasionally be positive in the familial or spheroidocytic form although in the main it serves to separate this from the acquired type.[5]

The serum bilirubin determination is often helpful when considered in relation to other findings. I will consider this in more detail subsequently.

The spectroscope is often helpful in the study of hemolytic disorders. With it one can easily and quickly detect excessive hemoglobinemia, methemoglobinemia, and hematinemia. The first of these three is associated with intravascular hemolysis generally, and the second and third with hemolysis due to chemicals or bacterial toxins. Hematinemia (or methemalbuminemia) is quite common in those states in which hemolysis is associated with liver injury. It is encountered in certain septicemias, notably that due to gas bacilli, and in a variety of liver diseases such as cirrhosis or severe hepatitis with hemolytic anemia.

Time does not permit me to dwell on the changes in the leukocytes and platelets which may occur in association with hemolytic disorders, but are of relatively little moment in diagnosis.

The sickle cell trait and spontaneous sickling of the erythrocytes are of well-known significance in relation to hemolytic disorders. Detection of the trait has been sharpened considerably by the finding that substances which reduce hemoglobin, such as sodium meta-bisulfite, rapidly produce sickling.[6] This is probably related to the recent finding of Pauling[7] that sickling is based on an abnormal molecular structure of the hemoglobin.

Before turning to the findings in the urine and feces in the hemolytic disorders, it will perhaps be well to dwell briefly on some fundamental concepts of bile pigment metabolism.[8] The fundamental classification of jaundice proposed by Rich[9] is quite helpful. In retention jaundice, bilirubin, which has just come from destroyed hemoglobin, accumulates in the blood, due either to overloading as in the hemolytic disorders, to relative sluggishness, as in constitutional hepatic dysfunction, or to actual injury of the liver cells. In this form, the serum bilirubin is characterized by a delayed or indirect van den Bergh reaction, and bilirubin is not found in the urine. In regurgitation jaundice, according to this concept, the bilirubin of the bile regains access to the blood. In this form, the van den Bergh reaction is prompt to a considerable degree, occurring within one minute after addition of the diazo reagent.[8] In this type bilirubinuria is characteristic, but in states of chronic jaundice

is usually not present until the level of prompt-reacting bilirubin is above 0.8 mg. per 100 cc. (the normal probably not exceeding 0.2 mg. per 100 cc.). The available evidence indicates that this type of bilirubin is simply a sodium salt while that in the serum in retention jaundice is bound rather tightly to protein. The belief that this is the original globin of the parent hemoglobin,[10, 11] must be strongly entertained.[8]

The bilirubin which enters the intestine in the bile is reduced by the bacterial flora of the colon to the colorless chromogen, urobilinogen.[12] Actually this substance is composed of two chemical individuals which are believed to be formed in sequence, the first being mesobilirubinogen, a considerable part of which is further reduced to stercobilinogen. These two compounds are best designated in the composite as urobilinogen. Fortunately they are characterized by an equally intense Ehrlich aldehyde reaction so that regardless of their relative proportions, the total urobilinogen may be measured by this means. A variable fraction of the urobilinogen thus formed in the colon is reabsorbed into the portal circulation and, under normal circumstances, is metabolized or partly re-excreted by the liver. In the presence of hepatocellular functional disturbance, urobilinogen returning to the liver in the portal circulation gains access to the general circulation in variable amounts and appears in the urine. Thus, in general, it may be stated that urobilinogenuria relates to liver function, while the amount of urobilinogen in the feces relates to the rate of blood destruction and to the presence and degree of interference with the outflow of bile from the liver. Insofar as hemolytic disorders are concerned, the first of these factors is much the most important and the one with which we are mainly concerned from the standpoint of diagnosis. The feces urobilinogen is often the court of last appeal in determining the presence or absence of hemolytic disease.

Thus it is evident that the detection of bilirubin in the urine and the determination of the amounts of urobilinogen in the urine and feces are often of considerable importance in the study of hemolytic disorders. The technique of the procedures have been discussed elsewhere.[13, 14, 15] The usual findings may be summarized as follows:

1. Bilirubin is absent in the urine in primary or relatively pure hemolytic states (retention jaundice); present in the urine in many secondary hemolytic states with hepatic disease (regurgitation jaundice). It may appear in the feces when there is very rapid blood destruction, due to incomplete reduction to urobilinogen in the colon. In such in-

stances, however, the amounts of urobilinogen are very large, so that there is no difficulty from a diagnostic standpoint.

2. Urobilinogen in the urine is often markedly increased, but it may be entirely normal in spite of a greatly accelerated rate of blood destruction. In the feces it is consistently increased, often 20 to 30 times the normal, especially in so-called hemolytic "crises."

Emphasis may be placed briefly upon the need of distinguishing hemoglobinuria and porphyria. In the intermittent acute type of porphyria characterized by abdominal and/or nervous symptoms, the urine contains the zinc complex of an abnormal porphyrin, i.e., the Waldenström uro-type porphyrin.[16, 17, 18] Such urines may be dark red, closely simulating hemoglobinuria insofar as gross appearance is concerned. The absorption spectrum is also extremely similar. However, the addition of a small amount of hydrochloric acid to the urine is quickly productive of the mineral acid porphyrin spectrum in the case of porphyria, which is easily distinguished from that of hematin in the case of hemoglobinuria. The former is characterized by a strong, well-defined absorption band at 552 mμ (max.), and a weaker one at 596 mμ (max.); the hematin absorption is rather broad and diffuse at 640 mμ (max.).

By way of illustration of some of what has been discussed in the foregoing, pertinent data from several instructive cases will now be given:

The first two cases stand in striking contrast to one another, in that the first had severe anemia without jaundice, and the second marked jaundice without anemia, yet both were examples of familial hemolytic disease.

Case 1. Male, 16. Hemoglobin 3.5 grams; icterus index 8; microcytes, increased fragility, marked splenomegaly. Reticulocytes 17 per cent. Feces urobilinogen 792 mg. per day; urine urobilinogen, a trace. Three weeks after splenectomy the feces urobilinogen was 91 mg. per day, the urine urobilinogen again but a trace.

Case 2. Male, 18. Splenomegaly, jaundice since infancy. Microcytes and increased fragility of the erythrocytes; mother has large spleen and frequent jaundice. Hemoglobin 13.6 grams; icterus index 94; van den Bergh entirely indirect; feces urobilinogen 705 mg. per day; urine urobilinogen 19.7 mg. per day.

In contrasting cases 1 and 2, it would appear that liver function was much more efficient in case 1, since there was no hyperbilirubinemia and no urobilinogenuria, while in case 2 the opposite findings are apparent. The inverse relationship of jaundice and anemia which is evident in these and other cases, actually suggests that a somewhat sluggish liver function may be a factor in minimizing or preventing anemia in this disease.

It will be noted that the icterus index is given in cases 1 and 2. At the time these cases were studied a number of years ago, the icterus index was being used in this laboratory, but has long since been replaced by the fractional serum bilirubin determination, which is more specific and informative, and, with a photo-electric colorimeter, almost as simple in execution.

Case 3.

♀, 26. Ictero-anemia and splenomegaly.

Hb. 3.2; R.B.C. 1.49; hematocrit 10%; MCV 91; MCC 33%

Fragility: H_1 0.50, H_2 0.32 (Control H_1 0.44, H_2 0.32)

Typical deeply staining microcytes in stained smears.

Date:	6-14-45	6-15	6-18	6-22	6-26	7-4	7-6	7-12	7-14	7-20	8-23
Retic.%	0	0.2	splen-ectomy	0.2	0.3	6.3	7.6	13.3	19.5	8.8	0.8

Bone marrow on 6-15 hyperplastic-normoblastic (ME*layer 15%)

SB*: 1′ 1.1, T 6.6 mg.% CC*2+ Liver biopsy: "Hepatitis"

Feces Ehrlich units 1720/100 gm. on 6-15-45

Feces urobilinogen 61 mg./day on 9-4-45

Case 3 is of particular interest because of the very low reticulocyte response prior to splenectomy and for some time afterwards, followed by a delayed rise, which was associated with the patient's recovery. The low reticulocyte count was obviously not due to marrow failure, as the marrow was hyperplastic and normoblastic; rather it must be attributed to some failure in the release mechanism. This case was also of interest in that the liver biopsy at the time of splenectomy revealed evidence of hepatic injury. This may account for the relatively high prompt-reacting serum bilirubin and the mildly positive Hanger test.

* ME=myeloid erythroid; SB=serum bilirubin; CC=cephalin cholesterol flocculation.

Case 4.

♀; 28. Severe ictero-anemia, orthopnea, anasarca.
Venous pressure 22 cm. Generalized cardiac enlargement, systolic murmur in pulmonic area. Palpable spleen, markedly enlarged liver.
Hb. 2.7; R.B.C. 1.0; hematocrit 8%; MCD 7.5
Retic. %: 4.0, 5.3, 2.0, 1.6, 2.3, 1.5, 1.0, 0.5, splenectomy, 0.6, 2.2, 1.5
Fragility: H_1 0.66, H_2 0.36 (Control H_1 0.46, H_2 0.34)
Bone marrow: hyperplastic-normoblastic (ME 18%)
SB: 1′ 1.0, T 2.4 mg. per 100 cc. (on admission)
Complete recovery following splenectomy

This case is also of interest because of the rather small number of reticulocytes. Cases 4 and 5 reveal that one cannot rely too wholly on an elevated reticulocyte count in making the diagnosis of hemolytic disorder, a point previously emphasized by Pepper.[19] The relatively high prompt-reacting serum bilirubin in case 4 was readily attributable to passive congestion of the liver.

Case 5.

♀, 23.
8-10-49: Variable weakness and slight icterus 2 years.
Moderate splenic and hepatic enlargement.
Hb. 9.5; RBC 2.7; hematocrit 32%; Retic. 12.2%
MCV 118; MCD 7.8
SB: 1′ 0.2, T 1.2 mg. per 100 cc. Coombs +
FE*: 1600 units per 100 gm.

Case 5 is of special interest because of the lack of any elevation of the serum bilirubin, the completely idiopathic character of the disease, and the positive Coombs test, pointing toward an acquired rather than a congenital or familial etiology. The osmotic fragility was normal.

Case 6.

♀, 37.
4-7-46: Weakness, pallor 1 month. Splenomegaly; liver not felt.

(Case 6 continued on next page)

* FE=Feces Ehrlich.

4-0-46: Hb. 3.5; RBC 1.3; hematocrit 11%; MCV 84; MCD 7.3: MCC 32%

Fragility: H_1 0.48, H_2 0.36 (Control H_1 0.48, H_2 0.36)

Date:	4-10	4-15	4-17	4-18	4-19	4-23	4-27	4-30	5-1
FE units/ 100 gms.	3280	3880	3600	4350	4480	splen-ectomy	1450	260	200
Hb. gm/ 100 cc.	3.3	4.0	5.1	5.2	3.8	5.7	10.5	9.7	10.1
Retic. %:	8.2		4.8	4.2	3.7		9.4	15.8	9.8

February, 1949: Apparent complete recovery

Case 6 reveals that a hemolytic anemia may at times be normocytic and normochromic without increased fragility, in spite of an unusually excessive rate of blood destruction. It is also interesting because of the remarkably *rapid recovery following splenectomy, and the persistent benefit three years later.* This case emphasizes that splenectomy should not be restricted to the spheroidocytic type.

Case 7.

4-17-44: Weakness, anorexia 4 months.
Jaundice 4 weeks. Marked pallor.
Splenomegaly; moderate enl. of liver.
Hb. 4.0 gms.; RBC 800,000; MCD 9.0 μ
WBC 210,000, 93 per cent lymphocytes.
Serum bilirubin 3.7 mg. Retic. 33%
Feces Ehrlich units: 1152 *per* 100 *gm.*
Complete remission following 25 transfusions and x-ray therapy to spleen.
4-12-45: Hb. 13.2; RBC 4.3 mill.; WBC 13,500, 84 per cent lymphocytes.
12-12-49: Hb 12.3, WBC 81,400, L97%; retic. 4.8%; feces, urobilinogen 306 mg.

Case 7 illustrates the value of the feces Ehrlich determination on a random sample; as a matter of fact in this instance the sample was obtained at the time of rectal examination. The patient was very sick and not having bowel movements for long periods. The marked elevation of the feces Ehrlich value clinched the diagnosis of hemolytic anemia, which of course was strongly suggested by the elevated reticulocyte

count. This is a striking example of the macrocytic hemolytic anemia which may occur with leukemia. Unfortunately, most of the cases in our experience do not respond nearly as well to x-ray therapy insofar as terminating the hemolytic activity is concerned. In some of our cases temporary benefit from splenectomy has been sufficient to justify the procedure.

Case 8.

♀, 18. Eclampsia. Delivery 3-29-49. (estimated 450 cc. blood loss)

Date:	3-23	3-30	4-1	4-2	4-7
Hb.:	12.3	8.9	6.7	6.4	7.3
Retic. %:				5.0	7.7
SB				1′:	0.4
				T:	0.6

Feces urobilinogen, 28 mg. per day, 4-4 to 4-8.
Submucosal vaginal hematoma discovered 4-7-49.
Prompt recovery.

Until the feces urobilinogen determination was made, this patient was thought to have a post-partum hemolytic disorder. The determination clearly revealed that this was incorrect, and a careful vaginal examination, which had been avoided because of the recent delivery, revealed the correct diagnosis. It might be noted that the fractional serum bilirubin in this instance was unlike a hemolytic and much more like an hepatic disorder in that the prompt-reacting fraction was elevated to twice the upper limit of normal while the total was well within the normal range. This was thought to represent a mild cholangiolar injury secondary to the hematoma and recent toxemia.

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DIAGNOSTIC TESTING IN PSYCHIATRIC PRACTICE*

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I.

PSYCHIATRIC practice, like practice in all other branches of medicine, needs diagnostic tests to supplement anamnesis and clinical examination. In psychiatry, even more than in other branches of medicine, the diagnostic tests are rarely specific for a disorder. In clinical psychiatry, even more than elsewhere in medicine, differential diagnosis is safer if several tests are available than if only one test is at our disposal. Psychodiagnostic tests, like other test procedures, rarely yield alone a dependable diagnosis and must therefore be viewed in the light of the data of anamnesis and clinical examination. Even more rarely than other tests in medicine can psychodiagnostic tests measure a process or propensity of the organism in its natural course; rather they expose the organism to standard stimuli and record the reactions. Psychodiagnostic procedures therefore resemble more the stress-tests (e.g., of cardiology) than the usual laboratory tests of medicine. Attempts at developing and clinically exploring psychodiagnostic procedures can be a potent tool in exploring organization and disorder of the personality. The quest after diagnostic procedures has often played such a role in the broad field of medical science.

It is easy enough to state the similarities of psychodiagnostic tests to other tests of medicine. It is quite a bit harder to state the differences. It is true enough that the medical laboratory can work with specimens taken from the body, while psychodiagnostics can deal only with various aspects of the total behaving organism. The final arbiter of all medical diagnosis is the autopsy, but there is no such final arbiter of psychiatric diagnosis, unless the psychiatric condition was a symptom of a neurological or glandular disorder.

The times have passed in which the difference could have been

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described by saying that medical diagnosis is not concerned with the total behavior of the organism while psychodiagnostics is. Today medicine *is* concerned with the total behavior of the body, though it does not always need to fall back on the study of the total behavior since it has diagnostic procedures approaching specificity. The difference lies rather in the frame of reference to which the behavior observed is subsequently related. Medical diagnosis relates it to the framework of physiology, psychodiagnosis to the framework of psychology. But even this distinction is tenuous, and not only because of the so-called psychosomatic problems.

My plan this evening is to dwell first, in brief, on what I just called the framework of psychology, in order to indicate some of the problems psychodiagnostics is up against. Then I should like to take two well-known tests, the Rorschach Test and the Bellevue Scale, and illustrate with them the nature and problems of psychodiagnostics. In closing I shall dwell on some of the future tasks of psychodiagnostics and on the relation of psychodiagnostics to medical practice.

II.

What is this framework of psychology to which psychodiagnostic data must be related?

Some 2500 years ago Heraclitus said: "man's character is his fate." In present-day language this means that the behavior of the individual is, in all its facets, regulated by a unique organization—his personality. Major and minor behaviors alike are regulated by the personality and express the personality. Thus we would expect that in principle every behavior should be usable as an indicator, a test, of the personality. Why this isn't quite so we shall see later on. Not only adjusted but maladjusted behavior, i.e., psychiatric disorder, is also an expression of the personality. It is one of the fundamental assumptions of present-day psychiatry that psychopathological phenomena are exaggerations, decompensations, of trends normally existing within the personality.

To view behavior in the framework of psychology means to ask, for every behavior manifestation: What is its place in the personality organization and how does it therefore express the personality and its pathology?

The time-honored method of psychiatric case history does exactly this. It obtains a description of a segment of behavior from the patient

and from informants, and treats it as a record of the past fate of the individual from which to infer his personality and its pathology. From the picture thus obtained it predicts future fate, i.e., prognosis.

Psychiatric case history and clinical examination have to contend with a burdensome abundance of behavior data, the sources, collection and evaluation of which inevitably involve *subjective* selection. It is in fact amazing how effective these tools become in the hands of people with theoretical training, gift of empathy, and experience. Yet besides being scientifically founded, the taking of a good case history and the giving of a good psychiatric examination are also an art.

The task of psychodiagnostics is to supplement case history and clinical examination by obtaining *objectively* selected behavior segments revealing of the individual's personality. The fact that every behavior segment is expressive of the personality does not make the psychodiagnostic job very easy. Experience with case history and psychiatric examination shows that an abundance of data, as well as a scarcity, can be an obstacle, since it necessitates arbitrary selection. This is not the only difficulty either. Consider one behavior segment: how a person handles a fork and knife. This behavior is highly stereotyped on the American scene—how revealing can it then be of the individual? Contrasting or in harmony with other behavior segments it is revealing, but by itself it would be a poor choice as a test sample of behavior. Take on the other hand facial expressions. They certainly show extreme individual variability and are very characteristic of the individual. Actually they are the means by which we intuitively judge people. But as a behavior segment they would be a poor choice for psychodiagnostics—they are so individual and so tied up with past history that comparisons between individuals can hardly be made by means of them, and the study of other additional broad segments of behavior is needed to decipher the many messages they convey about the individual's personality. Or take, e.g., this experience: a psychiatrist, deriding diagnostic tests, told me once that he could tell just as much about a man from the way his hat is crumpled—as any test could. Is "hat-crumpling" a good and revealing behavior sample? What about the people who do not have a hat along just then; what about those who have a new hat and did not manage to crumple it up definitively as yet; and what about those who just do not have hats?

The behavior sample psychodiagnostics can use for the purpose of

testing must be neither so broad as to be uneconomic or necessitating subjective selection, nor so stereotyped as to be empty, nor so idiosyncratic as to make comparison and interpretation unduly difficult; and last but not least, it must be ubiquitous—obtainable from any person at any time.

With these principles in mind let us visualize once more the problem of psychodiagnostics. In front of us stands a man who carries within the confines of his skin a unique organizing principle, his personality—what can we do to make it possible for him to reveal it to us? What we do is our test; what he reacts with is the behavior sample from which we expect information about his personality structure and disorder.

One more point about the framework of psychology before we turn to study, in the Rorschach Test and in the Bellevue Scale, the choice of behavior sample for psychodiagnostic purpose.

We are all familiar with the phrase: "this is just a rationalization." It is a psychiatric-psychoanalytic phrase that has invaded common parlance. What does it mean? We all know it means that the person addressed is accused of having a motive other than the one he stated. If we use the term correctly and are charitable, then we imply that he is not aware of this other motive. But the phrase implies for psychiatry something more, over and above this meaning. It implies that, as in physics there is an objective process of electromagnetic waves underlying the subjective experience of color, so in the framework of psychology there is an objective psychological process underlying both the subjective experience and the objectively recorded behavior. When we speak of personality organization we mean the totality of these underlying processes. —When we take a behavior sample it is not the *content* of the motor, verbal, etc., behavior which is the focus of our interest, because that may or may not be revealing of these underlying processes, i.e., the personality; it is rather the *form* characteristics of the behavior. E.g., in an Association Test it is not so much the content of a reaction word, but rather the reaction time and its relation to the stimulus word which are revealing of the process underlying the reaction.

The process underlying most behavior is a thought process, conscious or unconscious. The term "thought process" is used here in a broad sense which includes perception, imagery, fantasy, etc. Much of the theory of psychodiagnostic tests boils down to the study of thought processes. This is a field scarcely even mapped by academic psychol-

ogy, psychiatry or personality study. Only psychoanalysis has made some initial inroads.

Research in psychodiagnostic testing leads to new knowledge of these processes, and thereby to a better understanding of mental disease. In medicine the search for and the clinical validation of new diagnostic tests often brought better understanding of the disease. In psychiatry, where the concept of disease entities is still entirely in flux, psychodiagnostics is always as much a research job as it is a clinical service.

III.

I shall now describe and discuss two tests, the Rorschach Test and the Bellevue Scale. My purpose is not to describe them in detail, because these tests are probably familiar by now and the time available is insufficient. Rather, I shall illustrate with them the methods and problems of psychodiagnostics.

The Rorschach Test consists of ten symmetrical inkblots, some in shades of gray and black, others in bright colors. The cards are presented one by one in a standard sequence, with the question, "What does it look like to you?" The verbal responses and the reaction time are recorded. The responses are then scored. The scoring consists of five parts: 1) the area of the inkblot to which the response refers is scored, differentiating responses which refer to the whole card, to a well-articulated part of it, to a tiny, inconspicuous detail, etc.; 2) the content of the response is scored, differentiating responses of animal content, human, plant, inanimate, etc.; 3) those perceptual characteristics of the area which suggest the content given them by the subject are scored, differentiating responses in which form, or color, or shadings, or seeming motion, are most suggestive; 4) four degrees of accuracy with which the form of the area fits the content are scored; 5) finally the responses which are extremely frequent, or uniquely original, and those of peculiarly deviant verbalization, are scored and distinguished. These scores which represent the formal qualities of the responses, rather than their content, serve as the basis of interpretation.

What are the virtues of this test? A comparison with the case history or clinical examination will make some of them clear. First of all, it is a limited and well-circumscribed behavior segment which can be obtained from the overwhelming majority of patients, and can be fully recorded and numerically scored, allowing for direct comparison of

scores, both in the individual and between individuals. Secondly, the subject does not know what the significance of his responses is, a fact that reduces, though by no means eliminates, deliberate withholding as well as inhibition and blocking. Thirdly, even where withholding, inhibition, blocking or distortion of fact occurs, the consequences are different in the test than in the case history or clinical examination: in the latter we do not have before us the facts about which the patient talks or is silent; in the test the test-cards are the facts against which the responses, or lack of them, can be directly matched. Last but most important, the inkblots are unstructured material on which the subject readily displays his structuring, i.e., organizing principles and processes; the configuration of all these processes is unique to his personality. In giving life history or talking about any topic we are able to, and actually do, use our cliches and our book-knowledge for all they are worth. In fact it is part of normal adjustment to stay within familiar regions of experience and have well-prepared and therefore stereotyped responses to what we expect to encounter in them. The unstructured material of the test takes the person into unfamiliar regions and therefore tends to reveal his organizing principles, rather than only his ossified, well-established reaction patterns. Not that these reaction patterns are not important or individually characteristic, but they are not all that can or need be known about the person.

What are the outstanding limitations of this test? First of all, it is only one behavior sample and thus necessarily incomplete, even though it is one of the best, if not *the* best, we have hit on. In fact its degree of incompleteness varies with the personality of the subject. Secondly, though it eliminates the subjectivity in selection and organization of the behavior sample and makes direct interpersonal and intrapersonal quantitative comparisons of scores possible—its final interpretation can be no better than the actual experience and clinical knowledge of the psychodiagnostician. In other words, it is not a mechanical diagnosing machine, even though it has real safeguards of objectivity. Thirdly, in spite of the 28 years the test has been in use, there is still much that we do not know about it. The reason for our ignorance lies in the limitations of systematic clinical data, since comparison with such data is a most important way to explore such a test; and secondly, in the limitations of our knowledge of perceptual and thought processes which underlie performance on the test. The test has stimulated new and promising

work in both areas, but this is not the place to enter on that. Fourthly, this test, like other behavior samples, reconstructs primarily personality organization, and by itself need not give direct nosological information. This may actually be an advantage as well as a limitation, considering the state of flux of psychiatric nosology. Yet in the majority of psychotic conditions, depressions and schizophrenias, it tends to yield specific indicators and in the hand of the experienced examiner it is so far the best tool for diagnosis of prodromal, borderline or ambulatory schizophrenic conditions so easily missed clinically.

Let us turn now to the Bellevue Scale. This is an intelligence test consisting of the following eleven groups of items: *Comprehension:* e.g., what would you do if you found an envelope in the street that is sealed, stamped and addressed? *Information:* ranging from the simple question, "Who is the president of the United States?" to the extremely difficult, "What is the Apocrypha?" *Arithmetic:* ranging from simple additions to inverse proportions. *Digits Span:* immediate recall of 3 to 9 digits forward and backward. *Similarities:* ranging from, "How are an orange and a banana the same?" to, "How are praise and punishment the same?" *Vocabulary:* definition of words ranging from "apple" to "moist." *Picture Arrangement:* consisting of the arrangement of isolated pictures so as to form a meaningful story. *Picture Completion:* naming the parts missing in pictures. *Block Design:* construction of designs with blocks according to printed sample. *Object Assembly:* assembling simple jig-saws of a man, a head and a hand. *Digit Symbol:* putting symbols beneath numbers according to a sample.

Performance on each of these groups obtains a numerical raw-score. These raw-scores are translated into equated scores directly comparable with each other.

This test was designed to measure "intelligence" and does yield I.Q.'s. Indeed in clinical work we often need an objective appraisal of intelligence. It turned out, however, that it has uses other than the one for which it was designed. This is how it happened. It was noticed even before the advent of the Bellevue Scale that certain intelligence-test items tend to draw very poor performance from patients in general and from certain types of patients in particular. These findings, however, remained anecdotal and unused because of the structure of the tests in which they were observed. Let us not spend time on the test structures which tend to conceal these findings and see rather how the Bellevue

Scale reveals them.

In each item-group of this test the subjects face a set of problems of similar quality and graded difficulty. Thus it becomes obvious on what level of difficulty the subject fails, and since the item groups have equated scores, it is clear in which types of intellectual activity his performance rises above or falls below his other performances. The eleven scores can be plotted on a graph on which the degree of discrepancy of the scores from each other and from their central tendency is visually obvious. The study of such score relationships is called scatter or pattern analysis. Such analysis is feasible only on tests whose items are organized into homogeneous groups and in which the scores of these groups are directly comparable. The great advantage of the Bellevue Scale is that it fulfils these requirements. Its limitations are: first, that not all the item groups have a sufficient number of items so that their levels of difficulty are not always sufficiently continuous. Secondly, that it is not a sufficiently broad sample of those behaviors which we designate as intellectual activities. Thirdly, though clinically scatter analysis has proven itself a useful tool, our understanding of it is still extremely limited. The limitations are here again due in part to the unstable character of psychiatric nosology, terminology, and agreement in observation. In part, however, they are due to the limited amount of tested knowledge we have of so-called "intellectual activities." Scatter analysis has yielded already and promises to yield rich information in this area. On this point I should like to dwell in some detail.

We have seen that the individual performance on various item-groups can fluctuate; even individuals with identical I.Q.'s differ in their pattern of fluctuations, but the preëminent interest in the numerical I.Q. as such prevented discovery of the significance of these fluctuations. Yet we have striking experience in everyday life of these individual differences. We all know people of phenomenal memory who cannot remember numbers; others who have excellent judgment but quite unremarkable store of knowledge or memory; still others whose brightness is impressive though it stops at the simplest arithmetical calculation.

Scatter analysis attempts to create order in the jungle of these anecdotal observations. It assumes that performance in the various intellectual activities reflects the effectiveness of corresponding functions of thought organization, using this term again in the broad sense in which

I used it before. The effectiveness of these functions depends first on their developmental conditions in the course of personality development of which they are integral parts; secondly, on the specific interferences due to psychiatric disorder; thirdly, on the effects of the examination situation such as exacerbation of anxiety, tension, fatigue, etc.

It was possible, e.g., to demonstrate by scatter analysis that in hysterical-like personality organizations and conditions which are characterized by the prevalent defense mechanism of repression, the tested volume of remembered information is below the expected level of the subject. It has been shown that in compulsive personalities and obsessive-compulsive conditions characterized by the prevalent defense mechanism of intellectualizing, vocabulary and information will tend to be above the expected level of the subject. It has been proven that conscious anxiety impairs Digit Span, while tenseness replacing conscious anxiety tends to raise it above the individual's expected level. This test too, though in the main it indicates personality characteristics, has some highly specific diagnostic indications for schizoid disorders, for depressions, etc.

In scatter analysis we have found an avenue to grapple with the discrepancies among the intellectual assets of the individual and with their dependence on his personality organization. We have put this avenue to successful, if limited, clinical use.

The principle of this kind of testing is different from the Rorschach type of testing. In the Rorschach type the individual is faced with the task to organize an unstructured medium and he reveals thereby the organizing principles of his personality. In the Bellevue type he is to apply acquired skills, capacities, knowledge, etc., to reveal as it were relatively well organized and crystalized tools of his personality. In the Rorschach the organizing process itself is observed; in the Bellevue Scale it is auxiliary apparatuses which have crystalized from the organizing processes in the course of individual development. The Rorschach-type of tests are called projective, the Bellevue-type, non-projective tests of personality. These are complementary rather than competing tests. Combined use gives the greatest margin of reliability.

Using only the Rorschach one can get easily into the position of the legendary Eastern king. An Eastern ruler heard about the great man Moses and since he could not get Moses to visit him, nor did he have time to go to visit Moses, he sent his painter to paint this man

Moses for him. When the painter returned, the king called his astrologers and phrenologists and asked them to tell him what kind of man the painting depicted. The king knew Moses by his reputation as a leader of men, as a kind man, as a great man, as a gracious man. The phrenologists and the astrologers said otherwise. To them it was the picture of a cruel, greedy, self-seeking, dishonest, haughty man. When the king heard the report he cried out, "Either the painter does not know how to paint or there is no such science as astrology and phrenology." So off he went to see Moses and to decide the dilemma. When he reached Moses' abode and saw the man Moses, he raised his hands and cried out, "There is no such science as astrology and phrenology." Moses, very puzzled by this "how-do-you-do" asked him what he meant. When he heard the story, Moses shook his head and said to the king, "There is such a science as astrology and phrenology. Your astrologers and phrenologists told you truly what was in me. What they could not tell you was that by fighting against it I became what I am."

IV

The discussion of these two tests may have given you some feel for the nature and the problem of psychodiagnostics. I hope I managed to convey that though psychodiagnostics has a positive and important contribution *now* to psychiatric clinical work, it is a discipline in the very beginning of its development. Both the obstacles it has to cope with as yet and the possibilities it has in clinical work and research are vast.

The Rorschach and the Bellevue Tests are not the only ones widely used at present. The Thematic Apperception Test and various Association Tests are just as widely used. In work with borderline cases, psychotics, and cases of organic etiology, the concept formation tests, like the Hanfman-Kasanin and Goldstein-Scheerer, are generally used. In the diagnosis of personality, just as much as of mental disorder, it is a postulate of sound psychodiagnostic practice to use batteries of tests and not any single one; this postulate is no less important than that of using such tests *only* in conjunction with case history and clinical examination.

In the last few years it has been quite the rage to put out new psychodiagnostic tests. Many have been described in the literature, and quite a few have appeared even on the clinical scene. Some of these are promising, some are not. There are two points about these tests

worth making: 1) no single test by itself at present can do the psychodiagnostic job, and there is good reason to doubt that, short of a revolutionary discovery in psychiatric theory, a single test can ever be developed to do it. 2) My personal feeling is that there is so much that we need to learn about the tests we now have that it would be preferable if somewhat more of our total volume of ingenuity would go into that rather than into new tests. I realize, however, that creative genius cannot be stopped.

Finally, a word to those who wonder of what use psychodiagnostic procedures can be to medical men not experienced in psychiatry.

Tests are no better than the diagnostician using them. They do not replace psychiatric knowledge, case history and psychiatric examination. Therefore the general practitioner, unless specifically trained in psychiatry and psychodiagnostics, should have recourse to specialists in their use. Even psychiatrists familiar with these tests should prefer the help of specialists, for the same reasons which recommend comparable help in complex laboratory examinations.

In psychosomatic disorders, too, it will be preferable for the general or specialized medical man to deal with both the psychiatrist and the psychodiagnostician, since the findings of the latter may often need the evaluation of the psychiatrist in the light of *his* data. There *are* psychodiagnosticians trained and experienced in dealing with all psychiatric history and examinational procedures. They are, however, rather the minority and must be individually found. Such psychodiagnosticians will be capable of working directly with the medical man in diagnosis, research and even treatment of psychosomatic disorders.

How can the medical man recognize reputable psychodiagnosticians? They are clinical psychologists of professional standing and members of the American Psychological Association. They have been, or are being, certified by the American Board of Examiners in Professional Psychology. There is a determined effort being made to standardize the professional practice of clinical psychology. This effort is being carried on in consultation with the American Psychiatric Association in order to insure harmonious relations of these two closely related professions, and in order to plan jointly the combating of quackery and malpractice. It should be remembered, however, that standardization is a slow affair, studded with grandfather clauses and tolerance to a fault. In such a period a profession is best judged by the strongest and not by the weakest links in its chain.

JAMES EWING

*The man and the physician**

ELISE S. L'ESPERANCE

IT was with a sense of deep appreciation of the honor that I accepted the invitation of your chairman to give my tribute to the memory of the life and work of one of the most dynamic personalities in medicine in the past fifty years, whose life was so full and varied and who lived so energetically that one can gain only a fleeting glimpse of the greatness and simplicity of the man. No lines could be more fitting than those of Tennyson in his Ode on the Death of the Duke of Wellington:

"Rich in saving common-sense,
And, as the greatest only are,
In his simplicity sublime."

Every great man is entitled to have his shadow, and I enjoyed the rare privilege of working in the shadow of one of the most brilliant yet simple and human individuals I have ever known—Dr. James Ewing. My association with him commenced in the summer of 1910, and this sincere close friendship continued until his death in 1943. Those were the years of his greatest activity, as Professor of Pathology at Cornell University Medical College, where he was the inspiration and undisputed leader in that young institution, and as pathologist at Memorial Hospital where he transformed that institution into the most famous cancer center in the world.

His energy seemed inexhaustible and his enthusiasm in his subject could create a blazing interest in the most indifferent group of students. Through all the years I knew him he lived up to a motto he gave himself, "That whatever he accomplished would be by hard work and not natural talents."

I will not attempt to give a biographical memoir, which has already been so ably done by Dr. James Murphy, but rather to give you some personal impressions of the life and work of Dr. Ewing during those thirty-three years.

The events of Dr. Ewing's early life are of interest in the direct in-

* Given before the meeting of the Section on Historical and Cultural Medicine, The New York Academy of Medicine, November 9, 1949.

fluence they had in shaping his most distinctive characteristics: patience, persistence, and humility. He was born in Pittsburgh in 1866, one of a family of three. His father, Thomas Ewing, was a brilliant lawyer, a judge of Court of Common Pleas of Pittsburgh, a Scotch Presbyterian of the old school with high ideals and strict discipline. Dr. Ewing had great respect and admiration for his father, and said of him: "If I had any hereditary bents, they were intensified by the example of my father, of whom I may only say that he was a man of tireless energy, pure intelligence, and complete self-effacement"—qualities which are the dominant traits in Dr. Ewing's character also. His mother was of German descent, a studious scholar, a teacher, and a skilled musician. No doubt it was her influence that early developed in Dr. Ewing his extraordinary ability as a teacher and his love of good music.

Those of us who knew him can readily appreciate how a sensitive, active child brought up in this distinguished and severe atmosphere would acquire an urge to excel in all youthful sports. Unfortunately, this led to a serious accident which had a lasting effect on his entire life. When he was about twelve years of age he fell and injured his hip so severely that complicating osteomyelitis developed, so extensive that a consultation was deemed advisable. The family physician took him to Philadelphia and listened to the diagnosis and the verdict that a serious operation would be necessary. When the young boy was informed he promptly refused to submit to the operation and was taken back to his home and several years of painful invalidism, culminating in permanent disability.

His education was carried on by a tutor, Henry Gibbons, who later became professor of Latin at Amherst. Gibbons had a remarkable flair for languages and not only taught the boy Latin and Greek but, to quote from Ewing, "a marvellous way to balance delicate shades of meaning in Latin and Greek phrases; it was a lesson in close thinking which made a permanent impression on my mental processes." This clear and accurate way of thinking was one of his highly distinctive qualities. When he attended a medical meeting and the discussion became most involved he could solve the difficulty in one sentence.

His devotion to the microscope began when, as a young child interested in biology, he prepared a collection of mounted butterflies of such excellence that it was placed in the Museum of Natural History in Pittsburgh.

About this time he and his brother Tom had a pet dog. While they

were at school the dog died and when they returned home and found that the dog had been buried James Ewing immediately dug the dog up and performed his first autopsy. Even at this early age the scientific urge for investigation was clearly manifested.

In 1884, he entered Amherst College with very little experience in group study and competitive classes but he early determined to overcome this handicap by sheer hard work and intense concentration. During this period he came under the power of Charles E. Garman, of whom Ewing said: "He carried us through Hume, Kant, and Hegel to a firm belief in the theistic philosophy and gave us some immutable standards of right and wrong, two rather precious possessions." This crystallized his high standard of ethics and honor not only toward his medical colleagues but toward all with whom he came in contact. He graduated from Amherst in 1888 with high honors and that same year entered the College of Physicians and Surgeons at Columbia.

The microscope and scientific study still remained his guiding star. This brought him under the direct influence of that rare personality, T. Mitchell Prudden, then Director of Laboratories of the Alumni Association of the College of Physicians and Surgeons, and later Professor of Pathology there.

The close association with Prudden, resulting in a strong mutual admiration, was terminated only by Dr. Ewing's appointment as first Professor of Pathology at Cornell Medical College in 1899. However, their sincere friendship lasted as long as Prudden lived. Of his first paper, on "The Leucocytosis of Lobar Pneumonia," which he submitted to Prudden, Ewing said: "It was carefully prepared and I rated it as well nigh snow white, when I got it back it looked like the American flag. He used blue and red pencils." This event stamped the ideal of perfection in medical writing so clearly on Ewing that ever after his publications became masterpieces of clarity and literary skill.

Thus, under the guidance of Prudden he was taught to compose much meaning into a few words, and what was even more important, "that the pursuit of problems in a pathological laboratory is the choicest field in medicine." This instilled into the receptive mind of Ewing the belief that every piece of accurate research is very precious and that the student in this field deserves the most loyal support.

With this strong urge for the scientific side of medicine it is little wonder that after a few years of the unsuccessful practice of medicine he concentrated his life work in the field of research.

His interest in researches on the blood led him to write his first book—"The Clinical Pathology of the Blood," published in 1900, which was based on several years of experience as instructor in clinical pathology at the College of Physicians and Surgeons and periods of observation in the laboratories in Vienna and an intensive study of the blood picture in malaria at Camp Wyckoff during the Spanish-American War. This book, which he dedicated to Prudden, brought forth the following response: "I want to congratulate you on the appearance of your book, and the wealth of interesting and important lore which you have brought together." The book was remarkable for the thoroughness of observations and represented a critical study of the blood over a period of years.

When Cornell University Medical College was organized in New York in 1899, the Trustees sought an active well-trained young medical man to head the department of pathology, Ewing was selected and became the only full-time professor on the medical faculty. Here his association with such stalwart men as William M. Polk, Lewis Stimson, and Jacob Gould Schurman was very close. These men promptly built up a school of high efficiency, notable productivity, and the best traditions of medicine. The central figure and moving spirit in this enterprise was James Ewing. His clear vision, indomitable energy, and self-effacement provided the main spring for its development.

One of the saddest events in his life happened during this period—the death of his young and beautiful wife, after three years of marriage. Their short married life had been ideal. They had one son and anticipated the birth of another child when she developed a fatal toxemia of pregnancy. The shock to Ewing was so great that for a time it became an obsession with him to discover the cause and possible prevention of this disease. His report on the Pathogenesis of the Toxemias of Pregnancy was the result and served to focus the attention of investigators on the importance of further chemical studies of these toxemias.

Perhaps one of the most lasting effects of this tragedy on Ewing was to develop in him to an almost superhuman degree an understanding and sympathy for all suffering. Two months after the death of his wife he wrote to a friend, "When I married I thought I could do my wife some good, temporal and spiritual, yet she taught me how to live and showed me how to die. This was a marvelous service for one human being to do for another." There is no doubt his whole spiritual outlook on life was transformed by this catastrophe.

In the succeeding years he gradually replaced all pleasures and outside activities with an intense, almost fanatical devotion to his work, for he believed the only way to do superlative work was to make that work an obsession. In 1902, with the establishment of the Collis P. Huntington Fund for Cancer Research, a new avenue of approach to the solution of the cancer problem was opened up for him and he devoted himself wholeheartedly to the added burden of the organization of cancer research at Loomis Laboratory. In the nine years following, no less than thirty papers on cancer research were published and Ewing's reputation, not only as a cancer pathologist but as one of the authorities on cancer, was firmly established.

My first contact with him was in the summer of 1910 when I was to assume the position of assistant in the Department of Pathology. By previous arrangement I arrived at 9 a.m., with no idea of the duties required. At 5:30 p. m. he came into the laboratory just as active and energetic as if he had not completed an exhausting day's work and proceeded to dictate to me at a terrific speed his method for embedding very small bits of tissue for histological examination. When he asked me if I had ever had any experience in the preparation of specimens and I told him "No," he said: "You look intelligent. Now you are here, perhaps we can teach you. Here are two very valuable specimens and I have told you how to prepare them. Have them ready for me tomorrow morning." It was this complete confidence in the ability of his associates and those with whom he worked to carry out difficult tasks that made him one of the most stimulating teachers and created a spirit of loyalty and devotion among those who were privileged to come under his influence. This easily explains why no hours were too long or work too arduous for his assistants if it could be the means of acquiring knowledge of a subject which to him seemed so full of future promise in the difficult field of pathology.

The Pathological Department ultimately became the magnet to attract members of the faculty, distinguished visitors, and those seeking information. My room was immediately outside Ewing's office and many days there would be four or five persons waiting to see him. He was never too tired or too busy to give his opinion on a difficult pathological slide or to listen to an account of a new discovery that might be of aid in the diagnosis or treatment of cancer.

Early in his career at the college he started the nucleus of a library

for he felt that the greatest need for the future medical student was the ready access to the current literature. He often said that text books soon became obsolete, but the current reports would keep them abreast of the most recent discoveries in medicine. This library grew until it became a valuable asset in the Department of Pathology and later served the entire college staff.

Gross Pathology under Dr. Otto Schultz was a unit of the Department of Pathology. The important division of Bacteriology, although a separate department, still functioned under Dr. Wm. J. Elser in the closest association with Ewing. These three, Ewing, Schultz and Elser, formed a friendly group for the interchange of ideas, and with the cancer research work at Loomis gave Ewing an opportunity personally to supervise the interrelated research problems.

He felt that no pathologist could acquire the proper fundamental training without a careful study of the gross evidence of disease. Fresh specimens of the important diseases were not always available and this led him to organize a museum of rarer lesions preserved in natural color which could be used for demonstration in the teaching of students. His idea was to implant in the student's mind a relation between the history of a case, the gross appearance of the lesion, and finally the microscopic section. No wonder the students never missed their course in pathology. In fact, I am told that returning alumni always asked first to see Dr. Ewing, for he was the most beloved teacher.

Before 1912 Ewing had become convinced that the only way really to study cancer was in a hospital where accurate observation could be made on the life history of the disease in human beings. A fortuitous circumstance led to a meeting with Dr. James Douglas, the son of a physician, himself medically trained, and a brilliant scientist, who thought that the cancer problem was not being well handled, and who shared Ewing's views that the ranks of medicine should be enlarged and that medically trained men should be employed to develop the fundamental sciences for the solution of the problems of the sick. He wished to establish a cancer hospital in which men of investigative turn of mind should attack the problems of cancer in the human patient. To further this end he contributed $100,000 for the endowment of twenty beds, x-ray equipment, and a clinical laboratory in Memorial Hospital. Dr. Douglas was also keenly interested in the possibilities of radium in the treatment of cancer and he found an enthusiastic supporter in Ewing.

Together, with the coöperation of Dr. Polk, they reorganized Memorial Hospital as a specialized institution utilizing x-ray and radium as well as surgery in the treatment of cancer, and brought about an affiliation between Cornell University Medical School and Memorial Hospital, the first of its kind in New York. It was also the first attempt in this country to create a special institution for cancer and to emphasize the importance of cancer as a separate department in medicine.

Through ten years until 1919, with all his other responsibilities, he commenced and completed his classical book "Neoplastic Diseases." Prudden on receipt of one of the first copies wrote him a letter from which I quote: "This is the first work relating to medicine which I have fairly read or cared much to read in the last half-dozen years. I think your way of looking at tumors is most illuminating, and charged with common sense. You do not, as too many of us have done, let classifications lure you into pseudoscientific distinctions, which really get you no forwarder. And the wealth of stuff which you have woven in such a readable fashion into all your chapters is amazing. I suppose when the guy comes along who can tell us why and how cells are, we may talk wisely of the reason for tumors. In the meantime you have discreetly put the cards on the table and gone on playing the game. The pictures are bully. If the pathologist and his satellite, the practitioner, both don't sing your praises for this book, may the devil catch them both and treat the pathologist, at least, especially rough. I congratulate you." Not all of his colleagues showed the same appreciation; some looked for minute flaws in a masterpiece.

As acting librarian at Cornell at the time it was my privilege to share some of the long, arduous hours he spent on the preparation of this masterpiece. Few of those who read this standard work today realize that every reference, every photograph, and every detail of that book was done by Ewing himself. Many times it would be close to midnight when he would say to me, "It's time to shut up shop." That summer he wrote: "I spend most of my mornings at Memorial where cancer runs its uninterrupted course in large numbers. At night I do, as always, take a frugal meal at Osborn and read and write till 11:30. I admit it grows tiresome, but I am going to keep it up till this task is finished or finishes me."

Holidays and most of the Sundays were spent at the same driving pace. It is small wonder that this continuous tempo should have culmin-

ated in paroxysms of facial neuralgia which became increasingly violent in later years. Two serious operations failed to give the desired relief and it continued to plague him through the rest of his life. He once said, "This is the price I have paid for my book."

The decade from 1920 to 1930 was largely occupied with the expansion of the various activities at Memorial Hospital and with strengthening the affiliation between the Hospital and Cornell University Medical College.

Anyone who attended the weekly conferences at Memorial during this period felt the vast power and the clear vision which Ewing was giving to the problem of cancer. His continued emphasis on the need for clinical instructors, whose chief interest should be teaching and scientific medical investigation into the problem of cancer, had a far reaching effect. He felt that if you knew anything about cancer you should share the knowledge. This influenced him to sponsor actively all forms of cancer education and ultimately led to extending this education to the public, for he firmly believed that cancer prevention was not only possible but could be made practical. This accounted for his interest in the American Society for the Control of Cancer, of which he was one of the founders and most active participants. All these advances in medicine were accomplished by him while he served both as pathologist at Memorial Hospital and as Professor of Pathology at Cornell.

When in 1932 he retired as Professor of Pathology and became Professor of Oncology, to devote his entire time to the activities at Memorial Hospital, a very elaborate dinner was given to him by members of the faculty and alumni. It was a rather sad occasion, for all of them had deep respect and affection for him, but with his keen sense of the situation he began his speech with: "Well, school is out for me—the old bell has rung for the last time and I feel as free as air." It relieved the atmosphere of tension and did away with any feeling of bitterness among the many who loved him for his human understanding, for his high sense of honor, and for his tart astringent wit, which was never cruel.

He was director at Memorial Hospital from 1931 to his retirement in 1939. During this time he planned and strove for a new and more modern hospital to meet the requirements of a most complete cancer institute. He had proved the value of x-ray and radium in the treatment of cancer either alone or as an adjunct to surgery. He had attracted young medical men into this special field and, in the face of severe op-

position, had developed the idea of studying the effect of these agents on human cancer. The teaching of young people seemed to him of all things most important and it soon became known that opportunity was offered at Memorial to enter this field of cancer research.

Only those who knew him well realize the difficulties which surrounded every step in the expansion and recognition of cancer as a separate entity in medicine, and the effort entailed to have it occupy a place of equal importance with all the other branches of medicine.

The generous gift by Mr. John D. Rockefeller of the property at York Avenue and 67th and 68th streets crystallized his dream of a new Memorial Cancer Center to serve as a unique institution for research, education, and prevention in cancer.

Thus, the last ten years were filled with even greater activity; the designing of the most modern, scientific, complete, and adequate cancer institute; the raising of the necessary financial support; the safeguarding of the autonomy of Memorial Hospital while still maintaining the friendly affiliation with Cornell Medical College. These were problems that must be met and solved to the satisfaction of the majority of interests involved. They demanded patience, tact, and a keen insight into the future needs of the institution and required all of Dr. Ewing's splendid organizing ability.

Conference followed conference to the point of exhaustion and yet he always had time for an interesting section or a new theory of scientific value whether in chemistry, biology, or physics, for his interests were by no means limited to the field of cancer but included the whole science of medicine.

During these strenuous years he found the greatest relaxation in his favorite game of bridge—a game he did not play too well though he entered into it with the keenest enthusiasm and concentration. He never lost his interest in and was particularly devoted to tennis. He was an excellent player and except for his handicap would have qualified in competitive matches. He never missed one of the tournaments at Forest Hills. In fact, he organized the West Side Tennis Club and was its first president. As with everything he undertook, the club grew in stature and became of international reputation. He enjoyed swimming and was himself an expert swimmer. One of the things that delighted him was to invite his guests at Westhampton Beach to swim with him and then challenge them to swim to the second marker or barrel. Very few could

meet this challenge in the treacherous waters of the Atlantic Ocean, but he never failed to reach the goal. He had a beautiful automobile which he drove with great skill and speed. Such a drive was a thrilling experience for the passenger but I never knew him to have an accident, though at times one seemed imminent. There was very little in Ewing of the austerity considered a requisite in the public mental picture of a scientist, for he thoroughly enjoyed these infrequent relaxations.

He was a gifted public speaker and was much in demand for every occasion. This fact is remarkable when one remembers that in his college days, when invited to give the valedictory address, he refused at first because of timidity and nervousness. On the urging of his friend and professor, Dr. Garman, he accepted and gave the address and at that time determined he would accept every opportunity for speaking until he had conquered his self-consciousness. To overcome a handicap was one of his dominant traits.

His loyalty to his friends was phenomenal. Once he accepted you as a friend, nothing could change his opinion and he would find some extenuating circumstance for every failure. This was an exceptional quality and frequently proved the means of rebuilding an individual. The same loyalty applied to many of his laboratory possessions. His microscope had been his constant companion for many years and no modern attachment ever graced the stark simplicity of that monocular microscope. Occasionally a colleague would borrow it in the hope that in some way he would be able to read a section with the skill of the master. Ewing expressed his resentment of this foolishness by placing a heavy chain around the base of his microscope and padlocking it to his desk. Only a master in experience and observation could look through that brass tube at dead cells and read the future of the individual in a small bit of tissue removed from a lesion.

In 1938, his last year as Director of Memorial Hospital, he saw his dream realized in the completion and occupation of the hospital building on 68th street—a new modern hospital, beautiful in architecture, ample in space with facilities for research, and in close proximity to its affiliated Medical College.

One year later he became Consulting Pathologist to the Hospital devoting his time to revision of his book, the fourth edition, and granting interviews and conferences to all who came for advice or counsel. Occasionally he would see patients.

In 1941 he received an invitation to give a series of addresses in South America which he readily accepted, for he delighted to travel. The trip to South America was his last and he thoroughly enjoyed every moment of it even though he was nearly exhausted by the strenuous program planned. Three lectures in one day, hospital inspections, luncheons and dinners from 9 in the morning to 11:30 at night, and almost continuous air travel forced him to take a rest. But two days later he was ready for the trip over the Andes which was the most thrilling adventure. He was very proud to be the only passenger who did not need oxygen.

He received many honorary degrees: Doctor of Science from Amherst, University of Rochester, University of Pittsburgh, and Union University, and Doctor of Laws from Kenyon College and Western Reserve University. On his trip to South America each country honored him either with a degree or a medal. At home he received the Janeway Medal, the Clement Cleveland Award, and the John Scott Medal. All of these he accepted as a tribute not to himself but in recognition of the work to which he had devoted his life.

One of the honors which gave him the greatest personal pleasure was the gold headed cane presented by the American Association of Pathologists and Bacteriologists to the most distinguished *living* pathologist. In this recognition, as the Dean of Pathology, he followed Harold C. Ernst, William H. Welch, Theobald Smith, and Frank Mallory. He considered it as the highest tribute that could be given to an individual in the field of pathology.

In 1942, a bladder condition which had been considered benign three years previously developed increasing activity accompanied by distressing symptoms, and at operation a well-advanced and hopeless cancer of the bladder was found. From this, after a year of intense suffering, he died in May 1943, as courageously as he had lived.

The influence of his life, its human understanding and high ideals have left their imprint on all who knew him. His life work has given to American medicine an inspiration in cancer research that has established on a firm foundation the broad vision of cancer control today. There exist in every age masterful men who are masterful because they see with clear vision the course of events and fearlessly act upon the forecast. We wonder and cannot explain why these souls of rare genius have no successor of equal powers.

I think it is fitting at this time to give you Dr. Ewing's philosophy

of life, as illustrated by excerpts from a letter from which I have already quoted, written shortly after the death of his wife, to a colleague who had also experienced the loss of his young wife.

"We are called to the common heritage of suffering and we are brought face to face with eternal verities. In my sorrow though I reached high and low I have found only one thing that gave me any real comfort and that was an emphatic consciousness that this life cannot end all. I had drifted a good deal from things spiritual. I still realized that there must be a Power behind natural events and I always felt that this power must be intelligent or else lower than human. The Power cannot be less compassionate than the friends who try to help—otherwise man is the only creature which had better not be born and who has instincts that are false. Don't believe it. The instincts aroused by a great sorrow are not given to deceive us. On this point I don't want the opinion of the great philosopher, but the cry of the deep mourner. These are such immensely valuable lives. I fear we can only trust that they are better off than before. At any rate they are either annihilated or as Whittier says, 'They are safe in their immortality.' What a difference. I do not hesitate to accept my instinct that the latter only can be true. In which event we should not mourn our dead for their loss, but only for our own which is quite enough.

"So it seems to be a royal summons, this call to join the heroes and martyrs of history. It is a good deal that they are deemed worthy of the call. The great majority of natural deaths are preventable, if we would go back and do the right things at the right time. They are none the less inevitable with our human foresight. Don't entertain any doubts of this fact. We do the best we can at the time and the right choice is our good fortune, while failure is absolutely beyond our control.

"Perhaps it is because the depth of sorrow determines the possible greatness of joy. There can be no joy without sorrow and as I believe that this life doesn't end all, I take comfort in thinking of the day of recompense, when we shall give an account of the deeds done in the body. This is my religion."

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("Possession does not imply approval.")

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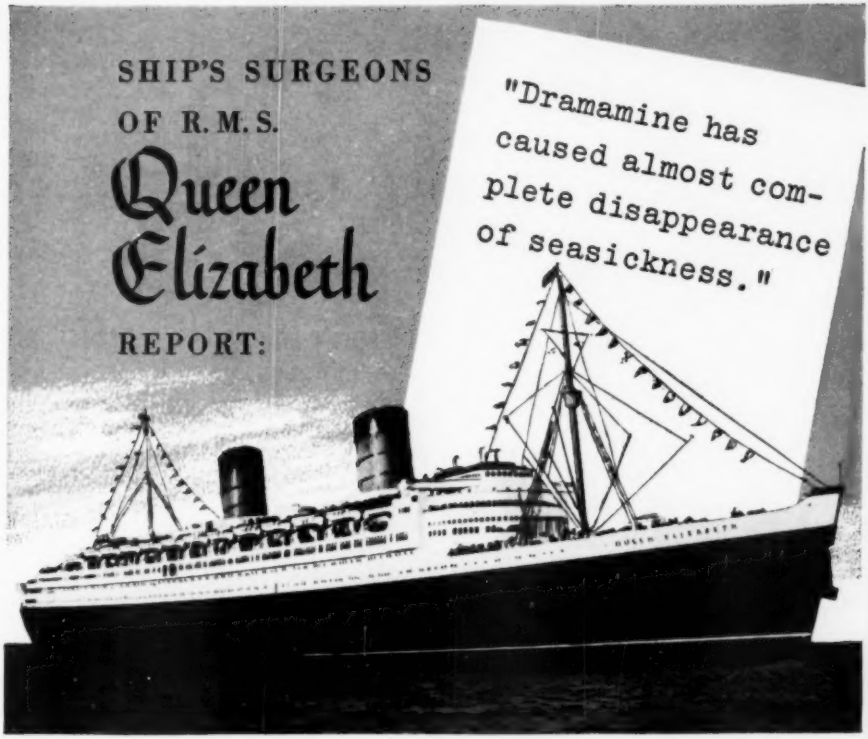

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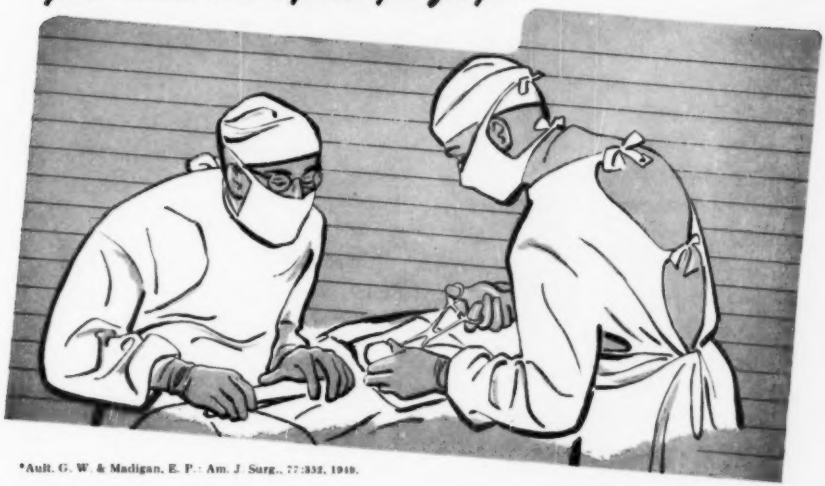

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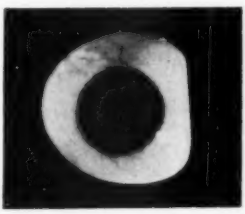

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FORMULA:

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. . . a potent chemical combination (*not a mere mixture*), combining Sulfathiazole and Urea in AURALGAN Glycerol (DOHO) Base—because it exerts a powerful solvent action on protein matter, liquefies and dissolves exuberant granulation tissue, cleanses and deodorizes, and tends to exhilarate normal tissue healing in the effective control of chronic suppurative otitis media.

FORMULA:

Urea	2.0 GRAMS
Sulfathiazole	1.6 GRAMS
Glycerol (DOHO) Base	16.4 GRAMS

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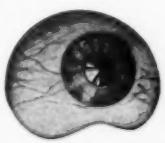

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Biolac is intended for prescription by every physician with infants among his patients. It satisfies the physician's demand for a complete food to which only vitamin C need be added. That means it is simplicity itself to prepare and provides the maximum in formula safety for the infant.

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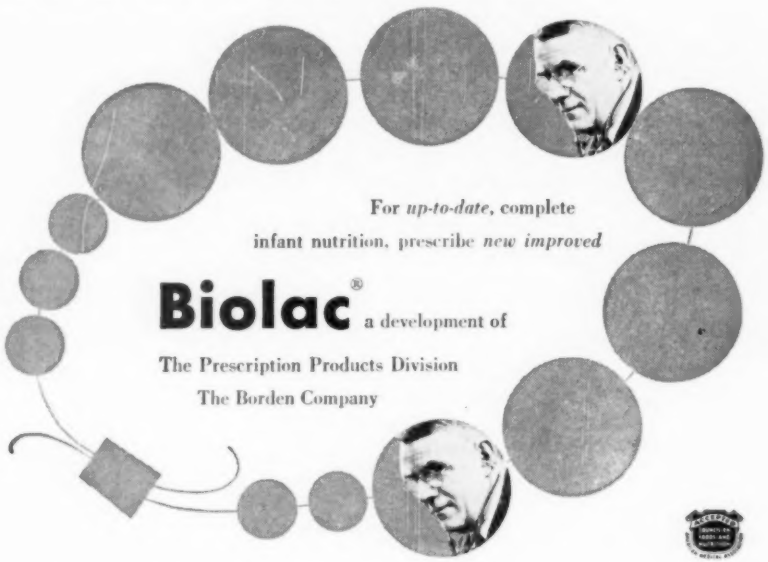


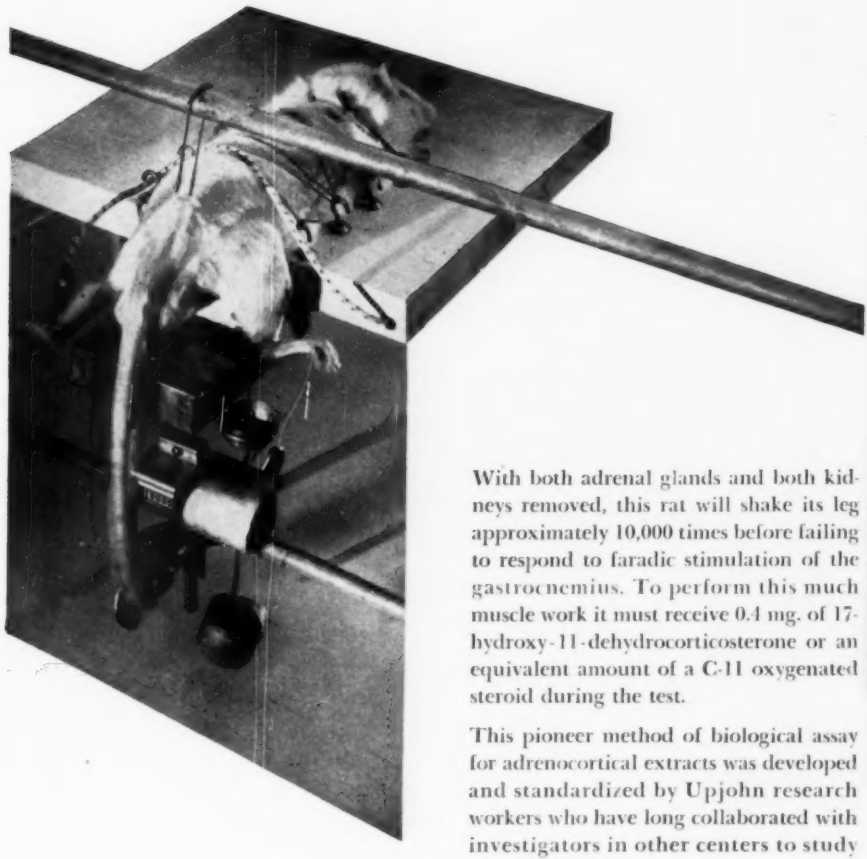
Ingredients: nonfat dry milk solids, dextrins-maltose-dextrose, lactose, coconut oil, destearinated beef fat, lecithin, sodium alginate, disodium phosphate, ferric citrate, vitamin B_1, concentrate of vitamins A and D from fish liver oils, and water. Homogenized and sterilized.

Dilution: one fluid ounce to one and a half ounces of boiled water for each pound of body weight.

Biolac is available at drugstores in 13 fluid ounce tins.

The Borden Company, Prescription Products Division, 350 Madison Avenue, New York 17

10,000 shakes of a rat's leg . . .



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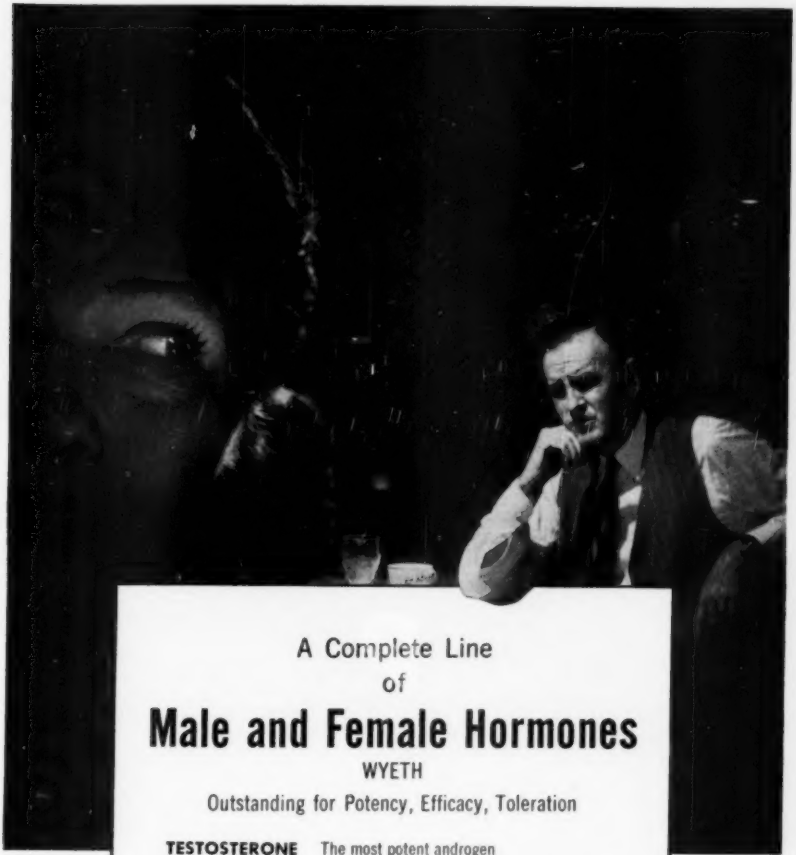

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